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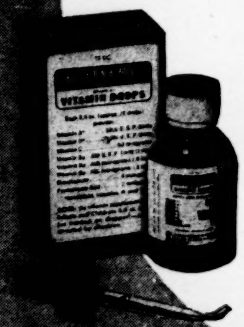

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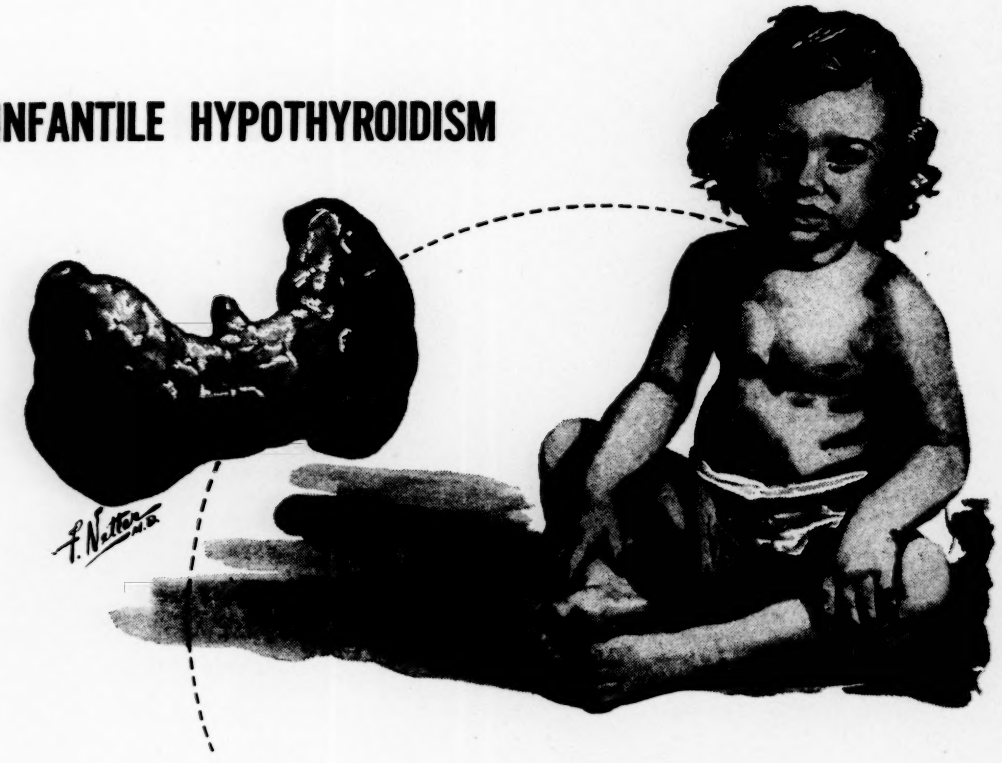

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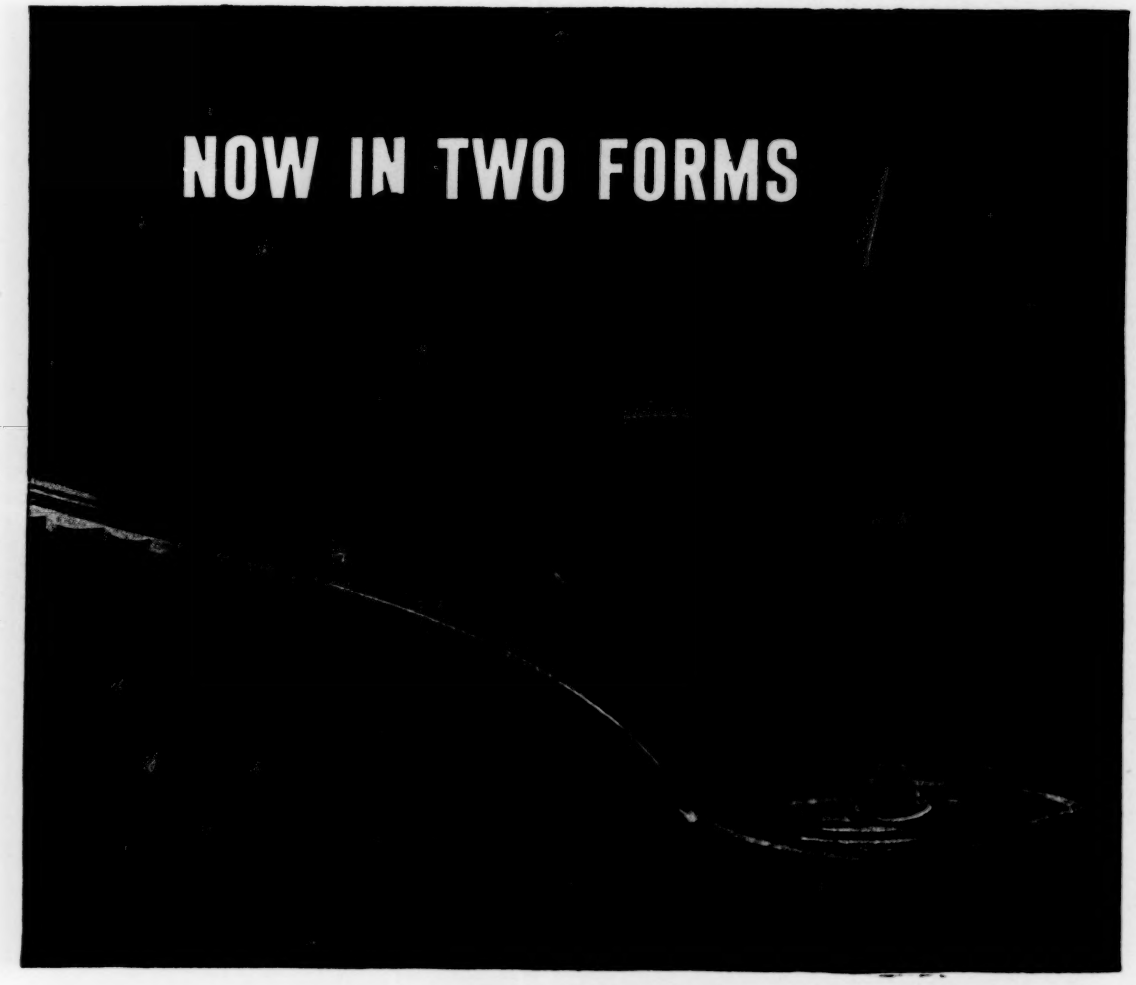

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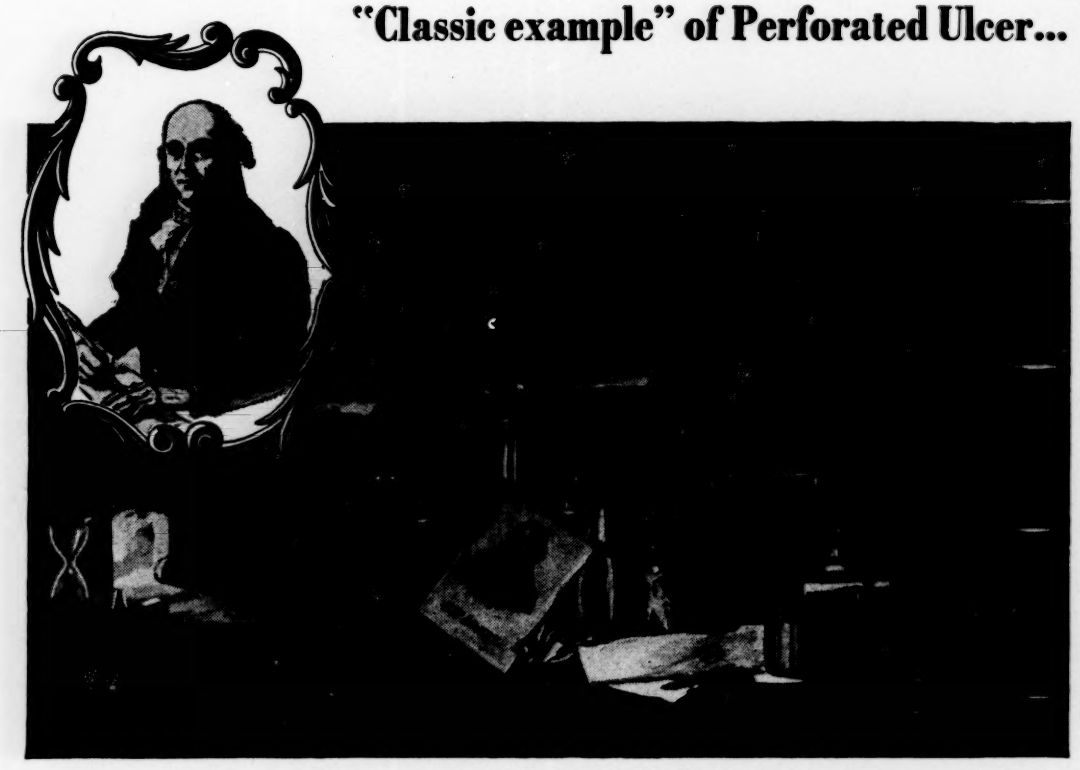

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[1] J.A.M.A. *135*:224 (Sept. 27) 1947.

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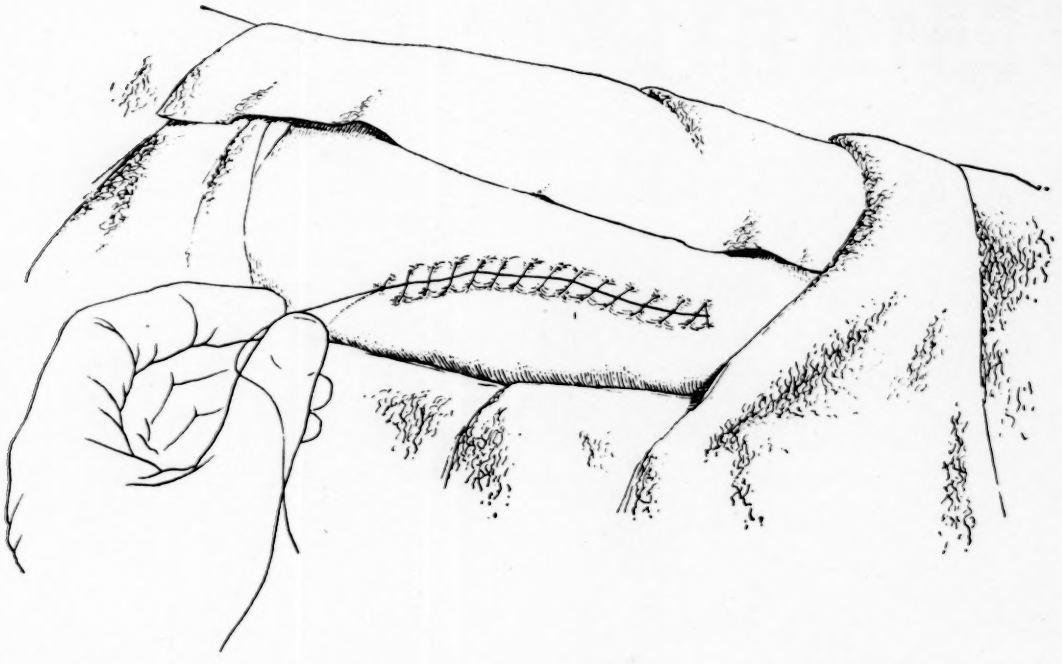

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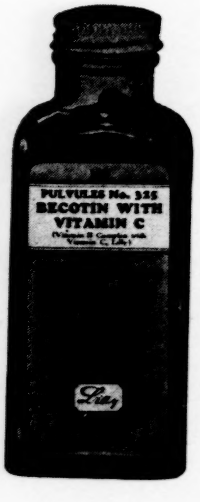

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The American Journal of Medicine

VOL. III DECEMBER, 1947 No. 6

Editorial

Ubiquitous Mycoses

THERE are extensive areas in the United States in which the residents are exposed to infection by pathogenic fungi. In these areas a large proportion of the population becomes infected at some time but symptoms may be entirely absent or so trivial in nature as to be overlooked. In most instances no harm results and all that remains is a specific skin sensitivity but, in some cases, healed pulmonary lesions are noted upon roentgenograms. Since the application of mass photoroentgen screening of population groups will probably increase (as the method is low in cost, easy to apply and efficient), increasing numbers of pulmonary lesions, of a type that were formerly called tuberculosis upon x-ray evidence alone, will be discovered. Thus it is necessary that physicians become more aware of the pulmonary mycoses, notably coccidioidomycosis and histoplasmosis.

The development of the current concept of coccidioidal infection is one of the more dramatic stories in modern American medical history. Coccidioidomycosis was recognized only as a rare, progressive and fatal granuloma until Gifford and Dixon[1–4] first demonstrated that the disease is essentially benign and self-limited. The recent addition of coccidioidal erythema nodosum, which is sometimes called "Valley Fever," to the clinical picture led to the development of an epidemiologic concept that Smith[5] has called a "true disease spectrum." The recognition that histoplasmosis, instead of being a rare and fatal disease, is a common and benign infection occurring over wide areas and in a large part of the population of some areas in the Middle West is of more recent occurrence. We may find, with increasing knowledge, that the epidemiology of histoplasmosis is not unlike that of coccidioidomycosis.

At the present time the knowledge of the biology of the coccidioidal infection is applied chiefly by physicians in the southwestern parts of the United States where the disease is common. It is known that most of the infections are not recognized and that the benign cases are infrequently referred to the etiologic agent. About one of twenty initial infections will result in coccidioidal erythema nodosum. The likelihood of dissemination or of a fatal outcome may be determined by quantitative studies of the blood serological reactions. The coccidioidin skin test is widely used and, for the most part, the reactions are interpreted soundly. During the training phases of the recent war large numbers of troops

[1] GIFFORD, M. A. San Joaquin Fever. P. 22. Annual Report Kern County Health Department for the Fiscal Year July 1, 1935 to June 30, 1936.

[2] DICKSON, E. C. Valley fever. *California & West. Med.*, 47: 151, 1937.

[3] DICKSON, E. C. and GIFFORD, M. A. Coccidioides infection (coccidioidomycosis). *Arch. Int. Med.*, 62: 853, 1938.

[4] GIFFORD, M. A. Coccidioidomycosis in Kern County. *California Proc. Vol. Sixth Pacific Sc. Cong. Pacific Science A.*, 5, p. 791. Berkeley, 1942. University of California Press.

[5] SMITH, C. E., BEARD, R. R., WHITING, E. G. and ROSENBERGER, H. G. Varieties of coccidioidal infection in relation to the epidemiology and control of the disease. *Am. J. Pub. Health*, 36: 1394, 1946.

were quartered in endemic areas. Controlled epidemiologic studies were made[6] and, as a result, we know the probable infection rate and the effect of season and of measures directed toward dust control upon the rate of primary infection in these areas. Our knowledge regarding the location of endemic areas has been greatly increased. The opportunity to study pulmonary lesions from their inception to their calcification was taken advantage of[7] and a great deal of information has been secured concerning the natural history of the common coccidioidal cavities. It seems quite probable from the epidemiologic point of view that similar studies upon the rate of attack and initial infections of histoplasmosis would be valuable if made in areas of the Middle West and it might be possible to obtain more detailed information about the clinical picture of the primary infection. It may well be that we are now uncovering another widespread and essentially self-limited disease caused by the fungus of histoplasmosis.

During the war years many hundreds of thousands of soldiers were exposed to coccidioidal infection in the widespread endemic areas of the Southwest. A certain number of these temporary residents have contracted the coccidioidal infection and frequently this has occurred without symptoms. In other instances the mild, initial symptoms have been overlooked or misinterpreted. Many of these individuals will be subjected to screening x-ray studies in the years to come. At Stanford University all new students have x-ray examinations of the chest and during the academic year of 1946 to 1947, clinical studies made upon students whose x-rays showed previously unsuspected lesions have revealed more instances of coccidioidomycosis than of tuberculosis. The number of lesions found which were considered to be due to histoplasmosis have almost equalled those which were considered to be arrested tuberculosis. Benign coccidioidal infections are probably now present in every part of the United States.[8] Physicians in all areas of the country will become more aware of coccidioidomycosis and of histoplasmosis; and it is hoped that when they are confronted by a pulmonary lesion, they will consider the patient's history of residence in endemic areas and will use the appropriate skin tests.

GEORGE H. HOUCK, M.D.

[6] SMITH, C. E., BEARD, R. R., ROSENBERGER, H. G. and WHITING, E. G. Effect of season and dust control on coccidioidomycosis. *J. A. M. A.*, 132: 833, 1946.

[7] JAMISON, H. W. A roentgen study of chronic pulmonary coccidioidomycosis. *Am. J. Roentgenol.*, 55: 396, 1946.

[8] KURZ, E. R. and LOUD, N. W. Coccidioidomycosis in New England. *New England J. Med.*, 237: 610, 1947.

Clinical Studies

A System for the Routine Treatment of the Failing Heart*

HARRY GOLD, M.D., NATHANIEL T. KWIT, M.D., WALTER MODELL, M.D., LAWRENCE W. HANLON,† M.D., MILTON KRAMER, M.D., SIDNEY GREENBERG, M.D. HAROLD L. OTTO, M.D., ELAINE W. COTLOVE, M.D., JOSEPH G. BENTON, M.D., MORRIS PEARLMUTTER, M.D. *and* WILLIAM ZAHM, M.D.

New York, New York

FOUR factors are generally considered of paramount importance in the management of the failing heart, namely, salt, water, digitalis and diuretics. Most current methods take account of these factors and put them into operation in special combinations through the use of various diets, several diuretic agents and digitalis preparations, administered in varying doses, intervals and sequence.

Several systems have been advocated in the literature. There are those in which digitalis occupies the central position. An attempt is first made to secure the results by digitalis alone, other factors being added when digitalis alone does not suffice. Methods are described in which exceedingly low sodium intake[1–4] is emphasized, and recently a system was proposed for the treatment of heart failure in which huge quantities of water play a conspicuous rôle.[5,6]

In the systems which are most commonly employed, the "low-salt" diet is prescribed, water intake is curtailed and considerable dependence is placed on oral diuretic agents, the mercurial diuretics being reserved for the more advanced cases with frank signs of edema or effusions and injected at inconstant and infrequent intervals. While the prevailing plans embodying these factors have taken us a long way from the days when the phrase, "rest, digitalis and futility," fairly described what was in store for the victim of congestive failure, the current plans and the methods by which they are applied seem still to leave the treatment of congestive failure short of the full potentialities for control.

The results obtained by the prevailing routines in the treatment of congestive failure have not been systematically evaluated in recent years. We have undertaken to make such an analysis of the results in 502 admissions treated by methods prevailing in four large hospitals, representing a fair cross section of the practice in New York City. We have compared these with the results obtained in 140 similar admissions treated by a system which we have applied in the past few years, involving the simultaneous use of digitoxin and measures for dehydration in which salt, water and the mercurial diuretics are balanced in a regimen conveniently applicable in a routine manner.

THE METHOD

Routine. The patient is put at rest, either in bed or in a chair, depending on the patient's comfort, unless there is some factor requiring bed rest alone, as in acute coronary thrombosis. Bathroom privileges are permitted if the patient is equal to the effort. The diet consists of 4 to 6 glasses of milk

* From the Department of Pharmacology of Cornell University Medical College, the Cardiovascular Research Unit of the Beth Israel Hospital and the Cardiac Service of the Hospital for Joint Diseases, New York, N. Y.

† David, Josephine and Winfield Baird Foundation Fellow.

daily and the water intake of 2 to 3 quarts taken in drinks of a few ounces at frequent intervals throughout the day. If no digitalis has been taken recently, a single dose of 1.2 mg. of digitoxin is given at one time. This is followed by a single daily dose of omitting those known to be especially high in sodium content. No salt is used in cooking and no salt is added at the table. This increase in the diet may produce slight and gradual increase in body weight. The daily dose of the mercurial is continued until the

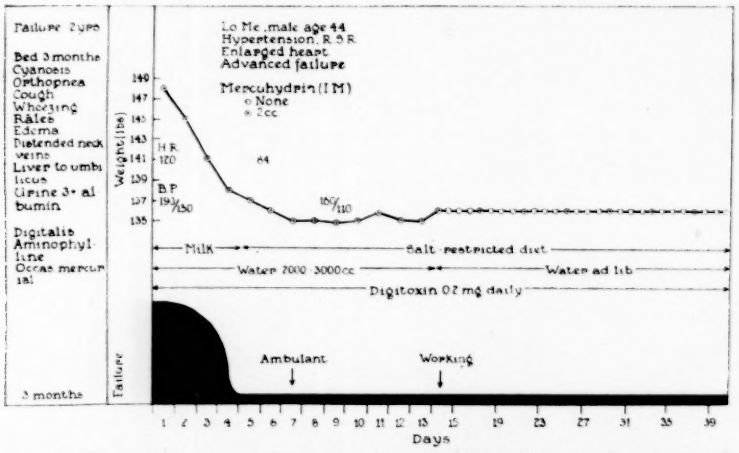

FIG. 1. Typical response of advanced congestive failure to the proposed regimen. The salt-restricted diet represented approximated 3 Gm. sodium chloride daily. The patient had been fully digitalized and was receiving a daily maintenance dose of digitalis before admission.

0.2 mg. The maintenance dose is increased or diminished according to indications. The patient is weighed at the outset and a chart is kept of the daily weight. A dose of mercuhydrin is given intramuscularly, 0.5 cc. on the first day. If there are no untoward reactions and the diuresis is insufficient, the dose is increased to as high as 2 cc. daily. The foregoing regimen is continued until all signs of edema subside and the weight declines to a resistant level, the "dry weight." At this point, the continued use of the daily mercurial fails to produce any substantial further reduction in weight. After a few days to insure that the "dry weight" has been reached, the patient may become ambulant and the treatment is modified to establish the maintenance requirements.

The daily weight is also the chief guide to adequate maintenance. In adjusting the regimen for maintenance, a more liberal diet is introduced, containing most of the common foods (eggs, meat, cereal, sugar, fruits, vegetables, cream, sweet butter) and weight shows a tendency to level off either at the original "dry weight" or at a somewhat higher level. The interval between the doses of the mercurial is then prolonged to every other day. If the weight level is maintained after a few doses, the interval is prolonged to every third day for a few days. This plan of prolonging the interval between injections is pursued until a point is reached at which a fairly abrupt rise in weight occurs on the day before the injection or a conspicuous fall on the day after the injection. One then returns to the longest interval which suffices to prevent these changes. In this manner, the maintenance plan for the mercurial is established.

In the course of time, it often becomes possible to liberalize the diet further and even prolong the interval between the mercurial injections. The maintenance of a constant body weight with only slight fluctuations and without any abrupt peaks of weight rise or fall is the primary indication that the maintenance regimen is adequate to insure against recurrence of congestive

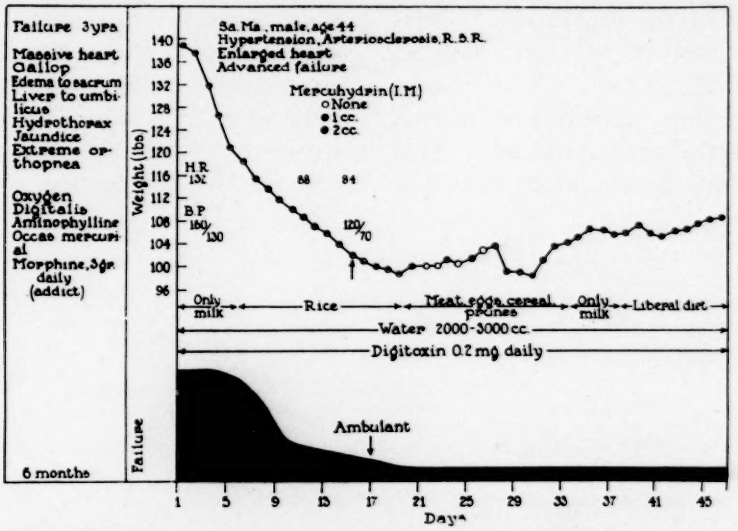

FIG. 2. Typical response of advanced congestive failure to the proposed regimen. The patient was a physician. He had been fully digitalized and was receiving a daily maintenance dose of digitalis before admission. The rice was added to the milk diet because he was distressed by his hunger. He had advanced pyorrhea and at the ↑ on the weight curve, bleeding from several sockets appeared which was difficult to control. The blood tests and prothrombin time were normal. The mercurial was suspected as the cause. After one week it was finally checked by local measures although the mercurial was continued. Note that the weight began to rise when the diet was increased and the interval between injections prolonged. The intensification of treatment proved that it was due to fluid. The patient became ravenously hungry and his weight again began to increase as a result of increased food intake. That it was not due to water this time was evident from the failure to lose weight with the more intensive system of dehydration (milk and the daily mercurial).

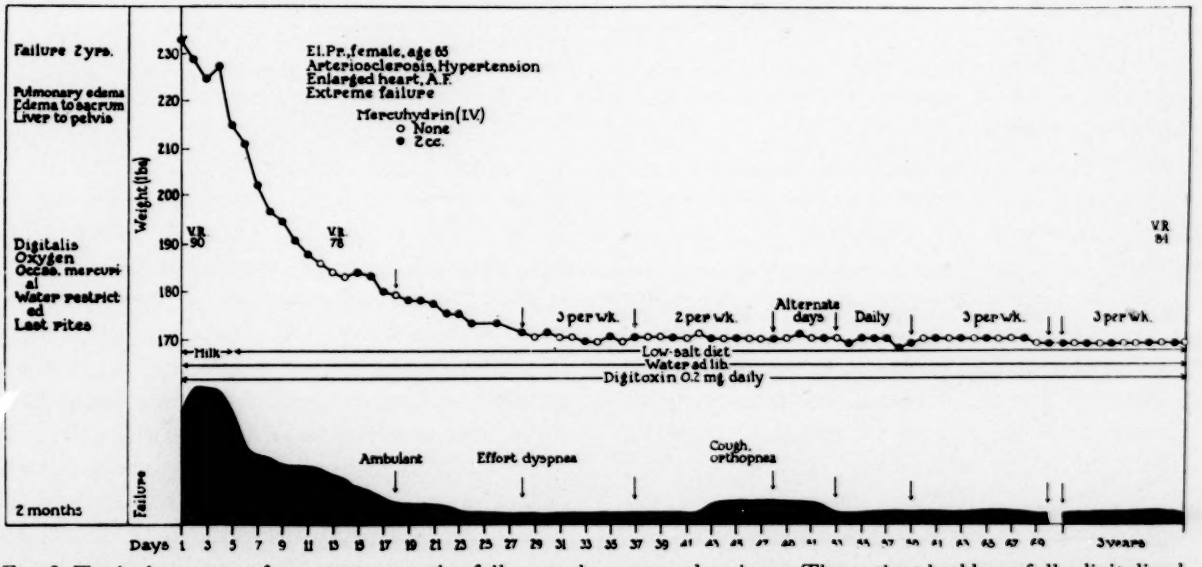

FIG. 3. Typical response of extreme congestive failure to the proposed regimen. The patient had been fully digitalized (to the point of vomiting and coupling) and was receiving a daily maintenance dose before admission. Note the intensification of symptoms in first four days of treatment; only the rapid fall in weight allowed the prediction that recovery was likely. Note the system of trial and error for establishing the maintenance program. The patient was working during the years of maintenance.

failure. This regimen is continued indefinitely. Illustrative cases are charted in Figures 1 to 5.

Special cases require variations in this routine. The size of the dose of the mercurial may be reduced and the intervals between doses prolonged with the appearance of the slightest evidence of excessive dehydration; and since the signs and symptoms are often indecisive at the beginning, it is well, when in doubt, to interrupt the dehydrating program temporarily. The case of acute coronary thrombosis requires special attention. Some of these patients develop pulmonary edema in association with the acute coronary thrombosis or, in the ensuing days, they develop shortness of breath and pulmonary râles with or without other signs of congestive failure. Digitalis alone is not very effective in controlling the failure in these cases. We apply the method outlined above except for the daily weighing. In addition to the other measures, the patient receives a daily dose of the mercurial until signs and symptoms of failure subside. The interval between injections is then usually prolonged to three days. This may be continued until it becomes possible to determine the necessary interval more precisely by the guide of the body weight. The subsequent course decides the need for the continued use of the mercurial diuretic. It is not un-

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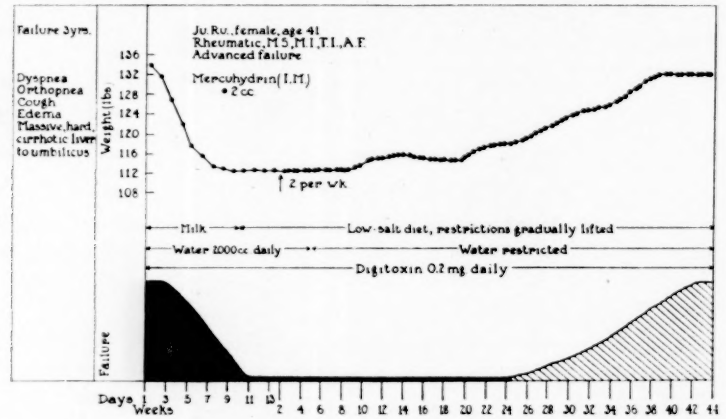

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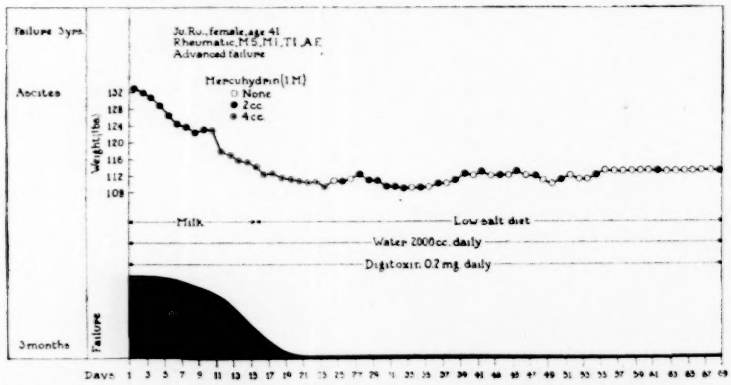


FIG. 4. Typical response of advanced congestive failure to the proposed regimen. The patient had been fully digitalized and was receiving a daily maintenance dose of digitalis before admission. Note that while the patient remained essentially free of former signs and symptoms of failure during the long maintenance period, the gradual increase of salt intake was accompanied by the appearance of ascites. (Fig. 5.)

FIG. 5. Same patient as in Fig. 4. Note that ascites was now the only sign of failure and that it takes longer to clear it than respiratory signs and edema. Note also the leveling off of the weight with the 2 cc. daily dose and the resumption of the decline when the dose was increased to 2 cc. every twelve hours.

common that, after recovery from the effects of the acute occlusion, these patients are able to carry on satisfactorily without any treatment for congestive failure.

In brief, five factors of cardinal importance are embodied in the proposed regimen: adequate salt restriction, liberal water intake, mercurial diuretics, digitoxin and a chart of the daily weight as a guide to the optimal state. The program calls for the application of these factors in two phases: (1) in the attack to abolish congestive failure and establish an optimal state and (2) in the long period of maintenance to prevent the recurrence of congestive failure.

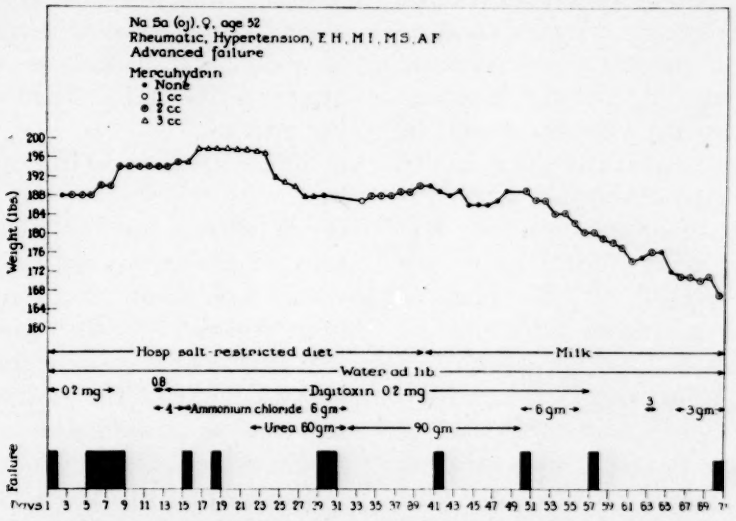


FIG. 6. Importance of adequate salt restriction in advanced congestive failure. Note that in spite of 3 cc. of the mercurial daily in addition to various oral diuretics, the loss of edema was insignificant until the salt was restricted to 1.5 Gm. by means of milk.

Diet. The prescription for a "low-salt" diet has now become a fairly common procedure in the treatment of congestive failure. The so-called "low-salt" diets of most hospitals contain anywhere from 3 to 6 Gm. of sodium chloride. This is too much salt for a great many patients with advanced congestive failure; and because of the wide variation in the salt intake from day to day with such a diet, the course of the response of the failure becomes irregular, the patient showing a fairly marked response on one day and almost none the next. This type of attempt at salt-restriction, in our experience, is unsatisfactory. There appears to be a wide gap between what is prescribed and what the patient actually receives. It is not at all uncommon that a patient on a so-called "low-salt" diet in the hospital finds his food so highly palatable that he, himself, becomes suspicious of its being literally "loaded" with salt, and the salt shaker not infrequently appears on the tray. This might suggest exceptionally incompetent dietary service, but the fact remains that, in relation to salt-restriction, these deficiencies prevail in abundance in the routine management of congestive failure in hospitals whose general standards of performance are otherwise considered very high. The traditional belief that salt is a harmless article of diet is not easy to overcome, and it will require a great deal of intensive education to impress upon the dietary and nursing services of hospitals the fact that an extra gram of salt may actually be a poison in many patients with congestive failure. The difficulties of securing a "low-salt" diet are not sufficiently appreciated by physicians; they often declare that their patients failed to respond even though they were on a "salt-free" diet without realizing how imperfectly the order for a "salt-free" diet was actually being carried out. (Fig. 6.)

It is for these reasons that we advocate the

use of milk as the sole article of diet in the early days of a course of treatment for congestive failure. The value of milk as a diuretic agent has long been known.[7,8,9] The 1 to 1.5 liters of milk a day supplies about 800 to 1,200 calories and from 1 to 1.5 Gm. of salt. The capacity for salt excretion is rarely below this level in cases of failure. Aside from a sense of hunger, most patients encounter no difficulty in taking this quantity of milk. They usually cooperate well in this restriction of diet, especially since, in the majority of cases, it is not necessary to continue it beyond five to seven days. The few patients who show special intolerance for milk, developing nausea or diarrhea, of course, have to be managed with one or another of the "low-salt" diets which are more troublesome to arrange.[1,5,10] In such cases, salt substitutes which are free of sodium, sprinkled on the food, may be used to advantage. For patients who are distressingly hungry with the milk alone, a bowl of boiled rice with sugar and milk several times a day may be added. Dry rice contains only about 0.1 per cent sodium chloride. There are about 350 calories in 100 Gm., and patients take from 200 to 300 Gm. daily in the so-called "rice diet" for hypertension.[11]

Supplementary Measures. There are several supplementary measures which are sometimes applied in addition to the foregoing regimen. Sedation is not used routinely but to meet special requirements. Patients in a poor nutritional state or those with massive edema, likely to lose 20 or 30 pounds of edema fluid, may receive supplementary vitamins, especially 10 or 20 mg. of thiamine chloride daily because intensive diuresis may result in deficiency.

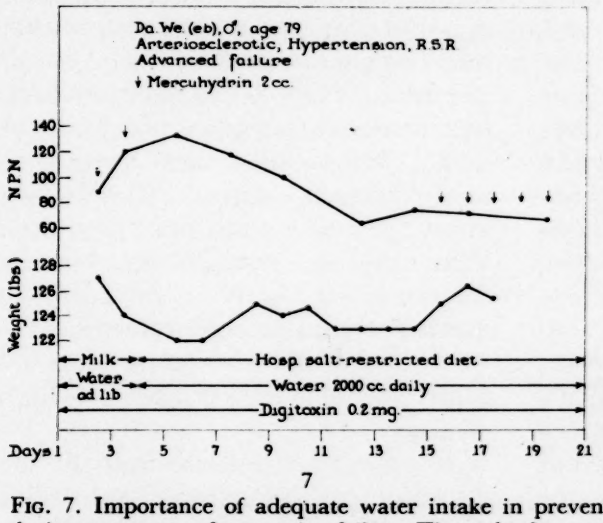
Water. In the traditional methods for the treatment of congestive failure, water intake is restricted. The extent of the restriction varies greatly. Most systems call for the reduction of water intake to about 1,000 cc. a day, and often the intake is as low as 500 cc. or less. Such restriction seems entirely natural to patients with edema who know that they have too much water in the body; many of them have been so strongly impressed with the danger of water that they are willing to endure much discomfort from thirst because of their conviction that water in the presence of edema is harmful. Indeed, this conviction receives support when the patient, inappropriately treated in other ways, allows himself a more liberal intake of water; for, unless salt restriction is adequate, a liberal intake of water will increase the edema.

There are several important studies in the literature relating to the problem of water restriction in cardiac failure. Since the details of the relationship between salt and water have been abundantly discussed and reviewed in the past few years,[1,2,5,10,12] it will suffice at this point merely to call attention to a few of the physiologic facts which serve as the basis for the procedure employed in the present study. A normal person taking a liberal quantity of water may excrete it in about four hours, but will take twenty-four hours or longer to excrete the water if salt has been added to it. The excretion of water is conditioned, therefore, by the presence of salt. A normal individual (quiet occupation in a comfortable atmosphere) requires about 1,500 cc. of fluid daily to make up for water losses (vapor, sweat, urine, stool) and prevent accumulation of blood metabolites or cellular dehydration; patients with damaged kidneys may require nearly twice as much.[13] The vast majority of patients with heart failure have no difficulty in excreting water *per se* but have a subnormal capacity to excrete salt.[1,2,8] The salt retention leads to water retention and edema. Whereas the average normal individual consumes and is able to excrete 10 or more Gm. of sodium chloride daily, the patient with heart failure in the more advanced stages may retain salt even if the intake is as low as 2 Gm. a day. When, in such a patient, the salt intake is restricted to the capacity for salt elimination, the quantity of water becomes a matter of indifference within limits; he will excrete it all whether the intake is 800 cc. or 3,000 cc. Water is a diuretic, and an effective plan for the treatment of congestive failure has

been described which includes the administration of water in amounts up to 6,000 cc. or more daily.[5]

In the treatment of congestive failure, therefore, it is clear that with appropriate salt restriction there is no need for water restriction; and furthermore, enough water must be given to maintain sufficient renal function to excrete the large quantities of extracellular fluid (edema) which is not only water but a solution of solid materials in water.

In the proposed regimen for the treatment of congestive failure, it is planned to allow a liberal intake of water sufficient to enable the kidneys to clear the blood of metabolites, taking account of the increased amount of such materials which come from the edema fluid. It is not intended that the water intake shall serve as a diuretic to any significant degree because for that purpose quantities are necessary which are troublesome to consume. Theoretically, the patient's thirst might decide the amount of water which is taken, but practically, such advice does not serve the purpose because of the tendency for patients with edema to take too little water, in spite of their thirst. In our experience, 2 to 3 liters of water daily can be taken conveniently and appear to be sufficient in the vast majority of patients with failure. It is surprising to learn how little water patients are apt to consume without special supervision. (Fig. 7.) In the plan of treatment, therefore, it is often necessary to request the nurse or the attendant to administer the water at fixed intervals in order to insure that a sufficient quantity is taken.



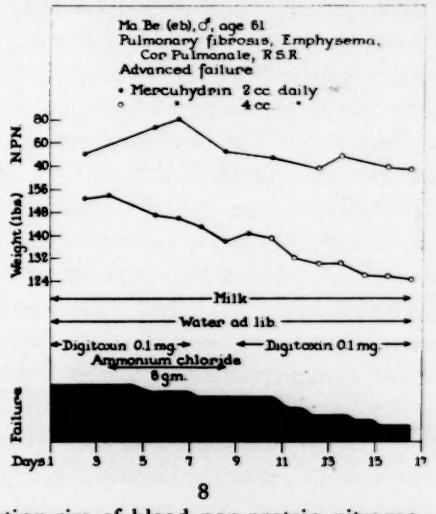


FIG. 7. Importance of adequate water intake in preventing rise of blood non-protein nitrogen during treatment of congestive failure. The order for water *ad libitum* resulted in an intake of only about 500 cc. daily and two doses of the mercurial were attended by a rise of the non-protein nitrogen from 83 to 133 mg., but during the intake of 2,000 cc. water daily there was no rise in the non-protein nitrogen after five doses of the mercurial.

FIG. 8. Note that with the 2 cc. daily dose of mercuhydrin the weight curve leveled off but resumed the fall when the dose was increased to 4 cc. daily. Note the temporary rise in blood non-protein nitrogen with a secondary fall even when the dose was doubled.

Digitoxin. Any one of a large number of digitalis preparations may be used to produce effective digitalization. For patients in extremis, the material may be given intravenously; a single dose of 0.4 mg. of ouabain, 1 mg. of digoxin, 1 mg. of cedilanid, or 3 U.S.P. units of any injectable digitalis preparations, such as digifoline, may be counted upon to produce a fairly high degree of digitalization. Additional fractions may be given at intervals of two hours if necessary.

In the vast majority of cases the oral route suffices, and for these, digitaline Nativelle or digitoxin is the material of choice. As has been shown in several reports,[14–17] this glycoside, after oral administration, develops

its full action as quickly as digitalis leaf or the tincture and its duration of action is the same as that of digitalis. While in the case of digitalis only about 20 per cent of the active glycosides are absorbed, the absorption of digitoxin is virtually complete. An average full digitalizing dose of 1.2 mg. may be safely given at one time to patients who have not recently had digitalis. This dose will produce a high degree of digitalization in about 75 per cent of the patients in congestive failure in a period of about six to ten hours. The incidence of systemic toxicity with this dosage is extremely small (less than 2 per cent). A therapeutically equivalent dose of digitalis leaf (1.2 Gm.) or the tincture (12 cc.) cannot be given in this way because the large quantity of non-absorbable glycosides will irritate the stomach sufficiently to cause nausea or vomiting in 20 per cent of the patients. In the case of the more tolerant patients, additional doses of 0.2 to 0.4 mg. may be given at intervals of six hours. A daily maintenance dose of 0.2 mg. serves the largest proportion of patients although in some the dose may have to be reduced to 0.1 mg. or increased to 0.3 mg. daily to maintain the optimum level of therapeutic effects.

For the case of those patients who have been partially digitalized with digitalis and for whom it is planned to turn to digitoxin, the potency ratio of 1 to 1000 is to be remembered; digitoxin is approximately 1,000 times as potent as U.S.P. digitalis by oral administration; 1 mg. of digitoxin may be used to produce the effect of 1 Gm. of digitalis.

Diuretics. Since an increased amount of extracellular fluid is characteristic of all patients with congestive failure, the indications for a diuretic agent exist in all of them. For oral administration, there are many such agents, namely, the xanthines, the acid-forming diuretics like ammonium chloride and urea. While some patients tolerate these agents fairly well, in the vast majority, tolerable doses are not very effective, and those doses which are sufficiently effective give rise to disagreeable symptoms in a high proportion of patients with failure. Urea is often necessary in doses as high as 90 Gm. a day. It has an unpleasant taste and such doses give rise to gastrointestinal symptoms and drowsiness. Ammonium chloride exerts its action by shifting the acid-base equilibrium toward the acid side. While daily doses of 3 to 4 Gm. are usually well tolerated, the more effective doses of 6 to 8 Gm. or larger not infrequently act as laxatives and cannot be continued for sufficiently long periods of time. Occasionally, an alarming state of renal acidosis results. Similar objections apply to the xanthines, theophylline or aminophylline. In small doses they are well tolerated but highly effective doses too frequently result in cerebral stimulation and gastrointestinal distress, so that their use must be discontinued after varying periods of time.

It is for these reasons that the mercurial diuretics are used almost exclusively in the proposed system of treatment. They are the most effective of all the diuretics. We prefer the intramuscular injection because of greater safety. The few recorded deaths with mercurial diuretics have all occurred with intravenous doses.[18,19] The danger of the intravenous dose, however, is relatively slight; and if the patient is one who reacts by the formation of lumps after the intramuscular injection, the slow intravenous injection may be substituted.

As to the site of injection, we usually prefer the muscles of the buttock, but it is well to explore other areas; many patients find the more accessible areas of the thighs and arms quite satisfactory for relatively painless injections. Emphasis should be placed on the need for making the injection deep into the muscles; the deeper the injection, the less is the likelihood of lump formation.

We prefer the preparation mercuhydrin to either mercuzanthin (mercurophylline) or salyrgan-theophylline (mersalyl and theophylline) because of the fact that it is less irritant to the muscle and is less apt to produce pain.[20] If the patient is hypersensitive to one of the mercurials and de-

velops allergic reactions, another mercurial diuretic may be substituted.[21]

The treatment is started with an initial dose of 0.5 cc. in order to ascertain the responsiveness of the patient and hypersensitivity. The most favorable plan is one in which the patient loses about 3 pounds a day. If this occurs with 0.5 cc., that dose is repeated daily. If the diuretic response is too small, the dose may be increased to 2 cc. daily. There are occasional patients in whom even the 2 cc. dose is inadequate or becomes inadequate after the first few doses. In that event, we have administered as much as 4 cc. daily, 2 cc. at twelve-hour intervals. (Figs. 5 and 8.)

The site of action of the mercurial diuretic is not conclusively established, but the best evidence indicates that it acts on the renal tubules to diminish reabsorption; and in view of the fact that there is a large increase not only in the total salt output but also in the concentration of salt in the urine,[22,23,24] diminished salt reabsorption may be a primary effect.

One of the most common unfavorable responses is weakness and muscle cramps. These are not usually due to the nature of the diuretic agent but to excessive diuresis and salt loss. Some patients may lose as much as 10 pounds of extracellular fluid from one injection without unpleasant symptoms whereas in others as little as a two- or three-pound loss at one time is excessive and results in intense weakness. The acute symptoms are sometimes overcome by half a teaspoonful of ordinary table salt. Their recurrence may often be prevented by the use of smaller doses of the diuretic. The common practice of prolonging intervals between doses in these cases is to be discouraged for this does not tend to eliminate the unpleasant responses. In point of fact, prolonging the interval between doses tends to increase the unpleasant reaction because it is the abrupt shift in electrolyte and water balance which gives rise to these symptoms; and after more fluid has accumulated, the diuretic response to a given dose may be larger. It is our practice to maintain the interval unchanged or to shorten it, but to diminish the dose so as to maintain a more or less constant diuretic effect without abrupt and extreme fluctuations.

One question which frequently arises is that of using the mercurial together with ammonium chloride. Since the object of such a combination is to enhance the diuresis,[25,26] we rarely use it; the mercurial alone suffices to produce all the diuresis that is necessary. If no weight loss occurs after several days on the routine, in which appropriate doses of the mercurial alone were used, ammonium chloride may be added.

The routine plan calls for a daily dose of mercuhydrin. This appears to be safe in the presence of an average normal urine flow. The excretion of the mercurial diuretic has not been extensively studied; but there are some unpublished experiments in the dog which show that about 90 per cent of the mercury may be recovered in the urine in a period of about six hours in the case of mercuhydrin, and observations in the rabbit[27] with salyrgan-theophylline and mercupurin indicate nearly complete elimination within twenty-four hours. In the extensive experience which we have had with patients in congestive failure and in patients with arterial hypertension without failure, there has been no indication of significant cumulation after daily injections of mercuhydrin for periods of weeks.

The possibility of renal damage or other toxic effects[28] by the organic mercurial often restrains physicians from its use. Although there are several suggestive reports of renal damage,[18,29,30] the evidence for irreversible injury of the kidney by the therapeutic doses of these non-ionized forms of mercury is far from convincing. We have now had experience with fairly large numbers of patients with congestive failure receiving 2 cc. of the mercurial two or three times a week for periods of from six months to three years, and 3 patients who had received a daily dose for periods of from two to three years, without evidence of renal damage. Others have reported long con-

tinued use of the mercurials without harm.[31] There is no evident contraindication to a dose of the mercurial in patients with congestive failure regardless of the state of the kidneys. Our system of continued mercurial administration has been applied to patients with all the common types of renal abnormalities encountered in rheumatic, arteriosclerotic and hypertensive heart disease with advanced congestive failure. We have encountered no convincing evidence of renal injury. We had one patient, a female, fifty-eight years old, with chronic glomerulonephritis and uremia (urinary casts, albuminuria, blood N.P.N. 216, creatinine 12.8, blood calcium 5.2, total proteins 6.1, A/G ratio 1.5, hemoglobin 7.9 Gm., CO_2 combining power 19 volumes per cent, ulcerative stomatitis, vomiting, optic neuritis, which had progressed to almost complete blindness, and muscle twitching verging on convulsions). This condition was complicated by congestive failure and pulmonary edema. The failure was controlled by digitalis and three intravenous injections of 1 cc. of mercupurin. After four weeks, she was discharged with virtually complete clinical recovery (free of symptoms, CO_2 combining power 43); there remained the laboratory findings of renal failure (blood N.P.N. 106, creatinine 5.6, blood calcium 7.8).

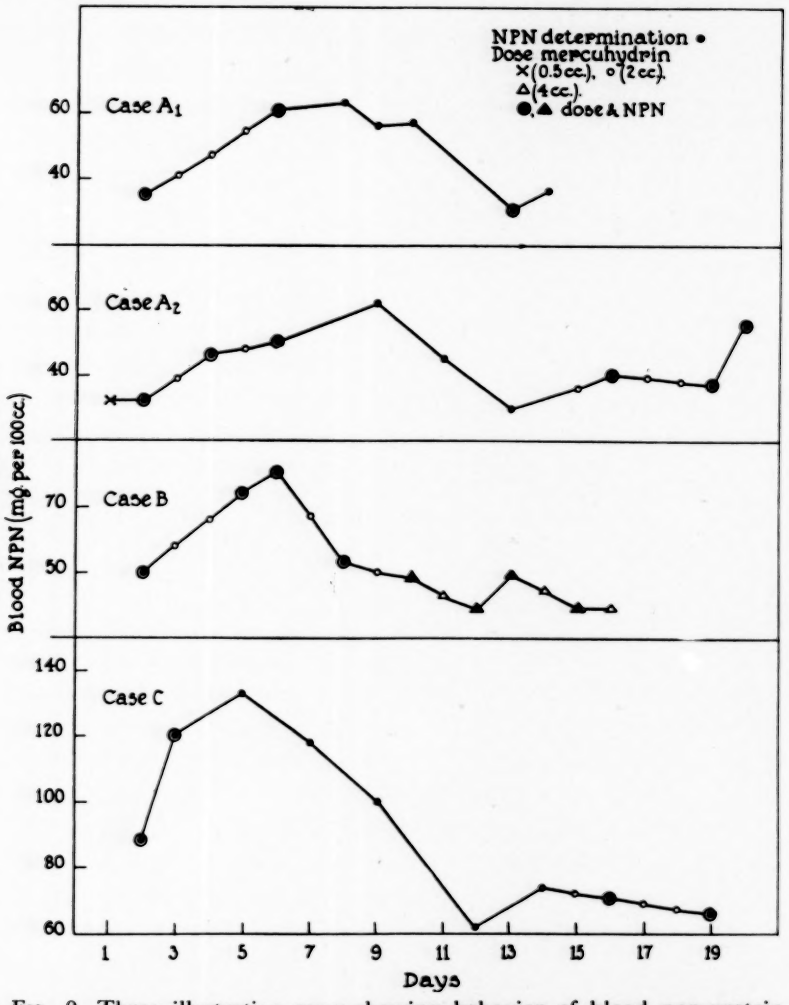


FIG. 9. Three illustrative cases showing behavior of blood non-protein nitrogen during the use of the daily dose of the mercurial in the treatment of congestive failure. Case A_1 and A_2 are repetitions in the same patient.

Whether the administration of the mercurial is continued in congestive failure will be decided by the nature of the response. Obviously, if a patient has a marked oliguria excreting only a few ounces of urine per day and a few doses fail to produce a substantial increase, there is no point in continuing. In the absence of a therapeutic response, toxic cumulation may occur. Attention should be called, however, to the need of making sure that the trial doses were adequate before the mercurial is discontinued.

The daily administration of the mercurial may result in an elevation of the blood N.P.N. Azotemia has been noted by others.[32] We have not followed the course with sufficient blood N.P.N. determinations in our cases to ascertain the frequency of this phenomenon. In a group of 133 patients treated with a daily dose of the mercurial, it was encountered in twelve patients. Figure 9 shows some typical examples. The mechanism of this effect is imperfectly understood. It is sometimes prevented by insuring adequate water intake. It may disappear during the continued use of the drug and sometimes even when the dose is increased. The effect appears to be reversible in much the same way as the action on the tubules which impairs reabsorption of salt and water, accounting for the therapeutic results. Within a few days after the mercurial is discontinued, the blood N.P.N. returns to normal levels. Until the mechanism of this response is better understood, it is well to follow the course with blood N.P.N. or urea determinations, especially in those cases in which the daily injection is to be long continued, and interrupt the dose for a few days if a marked rise occurs and tends to progress, resuming the injections at longer intervals.

One of the objections which has been offered to the use of the mercurial in our plan of treatment is the fact that it must be given by injection. The oral tablets and the rectal suppositories rarely suffice because in most cases, while small doses may be tolerated for a long time, adequate doses soon produce gastrointestinal distress, nausea, vomiting, diarrhea and abdominal cramps so that its continued use must be interrupted. It seems, however, that too much weight is given to the difficulty of the injection. It is well to bear in mind the similarity in the problems of diabetes and congestive failure. Both require continued injections to keep the conditions under control. There is little more trouble in the injection of the organic mercurial than in the injection of insulin. After an appropriate system of intervals has been established by the physician, a member of the family and sometimes the patient can make the injection of the mercurial with little or no danger.

Guides to Treatment. The guides to the treatment of congestive failure, which are employed in most current methods, are the patient's symptoms, the extent of the edema and a charting of the fluid intake and urine output. These are, on the whole, unsatisfactory in our experience. The patient with far advanced congestive failure may, in the early days, show no appreciable amelioration of symptoms with a system of treatment which is eminently satisfactory. The absence of early relief of symptoms often leads the physician to abandon a course of treatment which, if pursued, would have produced the desired results. (Fig. 3.) Fluid balance charts are notoriously misleading. At their best, they fail to take into account variations in visible and insensible perspiration and other sources of water loss. At their worst, and much of such charting approaches that state quite closely, the quantities of fluid or urine are estimated rather than measured and many of the fractions fail to be recorded. It is a time-consuming and troublesome nursing procedure which does not yield information justifying the effort; as a routine in the treatment of congestive failure, it should be abandoned. In its place, we employ a chart of the daily weight. Most patients with congestive failure are equal to the effort of a daily weighing. Long before symptoms improve or gross signs of edema have changed, the declining body weight reveals that the treatment regi-

men is effective (Fig. 3) and allows the prediction that the failure will be brought under control; and conversely, a leveling off of the curve of weight loss, while edema persists, indicates at once the need for intensification of the treatment. (Figs. 5 and 8.) The treatment of congestive failure without an accurate record of body weight is comparable to the treatment of infection without a fever chart, or the treatment of auricular fibrillation by digitalis without a record of the changes in heart rate, or the treatment of diabetes with insulin using only symptoms as a guide and no record of changes in the ketonuria or glycosuria. Without this record of weight, the treatment of congestive failure is deprived of all the precision that is otherwise possible. (Fig. 10.)

The current routine treatments of congestive failure are not systematically guided by the chart of daily weight. In the 502 admission for congestive failure, which we shall discuss presently, there were only 2,299 weighings for a total of 11,873 hospital days, or a weighing on less than 20 per cent of the hospital days. Of these 502 admissions, 51 per cent were not weighed at all; and in the remaining 49 per cent, who had some weighings, the interval between them averaged 3.1 days. Since it is not often done, the technics are poorly developed. Those who have not been in the habit of prescribing a daily weighing for their patients with congestive failure have an interesting experience in store for them when they begin to write such orders and begin to depend on the record from day to day; either the scale is out of order or inaccurate, or it is not readily accessible to the patient, or there are not enough scales for the number of patients, so that it becomes impractical to weigh at approximately the same time each day, or the patient is frequently weighed on different scales varying in adjustment by several pounds, or the nurse forgets to weigh the patient every day (although a lapse in the daily temperature recording is a rare occurrence), or the nurse weighs the patient but fails to record it or records it among the nurse's notes making the daily inspection of the course too time-consuming to be useful. To weigh a patient accurately daily and to keep an accurate chart of the weight seems to be either a lost art or one which has never been well developed.

The objective is to reduce the body weight to a level at which the optimum volume of extracellular fluid remains. In actual practice, the proposed system is continued until the patient ceases to lose weight. We term this the "dry weight." Many patients are most comfortable at that level. In others, the "dry weight" represents excessive dehydration and the patient feels stronger at a level a few pounds above it. The character of the symptoms helps to decide the weight at which the patient will be maintained.

Lapses in restrictions are extremely common. They are revealed in an abrupt rise in weight usually long before any symptoms occur, although in patients with predominantly so-called "left heart failure" an increased dyspnea or othopnea sometimes precedes a significant rise in weight as evidence of lapse in treatment.

In the long period of maintenance, the problem sometimes arises of distinguishing an increase in body weight due to improving appetite and health from that due to water retention. An abrupt rise of a pound or two is strongly suggestive of water retention. When there is doubt, the problem can frequently be resolved by intensification of the treatment through a daily injection of the mercurial. (Fig. 2.) If it is good body tissue, such a measure is apt to produce little change in the sustained level of the body weight. (Fig. 11.)

Maintenance. The need for an effective system of maintenance after recovery from an attack of congestive failure is self-evident. Unless that is done, the patient again passes into congestive failure. Among the 376 patients with congestive failure treated with the various current routines, there were sixty-nine patients or 18.2 per cent with multiple admissions to the same hospital for the treatment of failure. The number of admissions varied from two to eleven in different patients, an average of

2.8 admissions per patient at an average interval of 8.2 months. There are many causes for the recurrence of attacks of failure. The majority of recurrences are preventable. Lack of cooperation on the part of the patient is not an uncommon cause but we

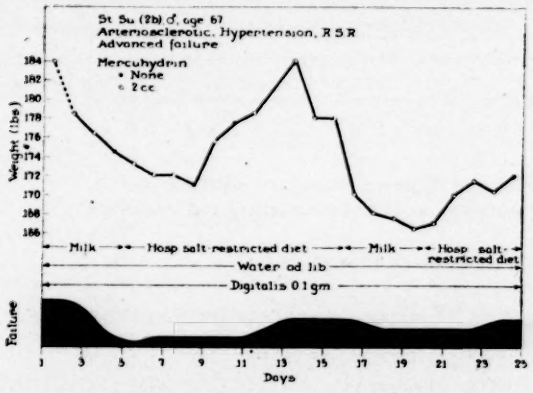


FIG. 10. Importance of daily weight as guide to treatment in congestive failure. Note that the daily mercurial and the milk diet caused prompt recovery; there was prompt relapse when the interval was prolonged and the salt intake increased. Note that the sequence of adequate and inadequate routines was repeated and the patient was well on the way to a third attack of failure at the time of discharge. Although the patient was weighed, the record was not used as a guide to therapy.

believe that a very considerable proportion of the recurrences may be assigned to the inadequacy of the therapeutic plan for maintenance with which the patient is provided. In the most common current practices, after the patient has recovered from an attack of failure the diet is made more liberal, although salt may still be restricted and digitalis is likely to be continued; but there are two common failings, namely, dependence is placed chiefly on oral diuretics, if they are used at all, and the patient's symptoms are used as a guide to adequacy of treatment. The oral diuretics are usually insufficient and to discover that the treatment is inadequate when symptoms appear is too late. A frequent modification that is equally bad is to have the patient return for an injection of a mercurial when the legs begin to swell or suffocation appears at night. These are not systems of maintenance but of retreatment of failure. The omission of the maintenance schedule of the mercurial diuretic is a frequent cause of recurrence of congestive failure. (Fig. 12.)

It is our practice to depend on the same five cardinal factors in maintenance as during the treatment of the attack of failure: Salt is restricted, water is taken freely, a

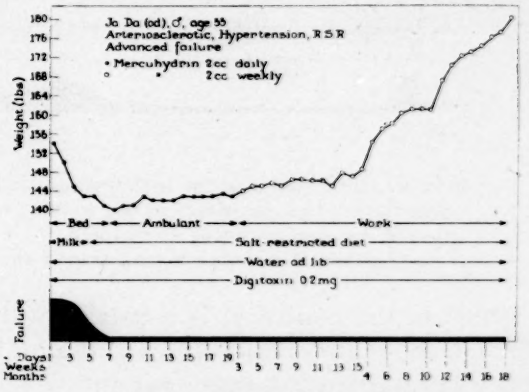


FIG. 11. Typical response of advanced congestive failure to the proposed regimen. Note the period of 1.5 years of maintenance with 2 cc. mercuhydrin per week; weight gradually rises due to good body tissue, not significantly lowered by periodic trial with daily doses of the mercurial. Compare with Figure 12.

daily dose of digitoxin is continued and the intramuscular mercuhydrin is continued. The charting of the weight serves as the guide. The details vary from one patient to another and the final plan for any one patient is determined by the method of trial and error. The objective is to discover the most liberal diet and the longest interval between injections of the mercurial which will serve to maintain the patient's weight at a constant level or with slow rise which is not lowered by intensification of the treatment. The various measures are interrelated and may be balanced. The patient often has a choice of maintenance plans such as a highly unpalatable diet containing only 2 Gm. of salt a day together with only one mercurial injection a week or a combination of a very liberal diet with a mercurial injection every other day.

At this point, attention should be called to a common misconception regarding the manner in which the mercurial functions during the maintenance period, namely, the belief that the mercurial fails to serve a purpose when the dose fails to produce a fall in

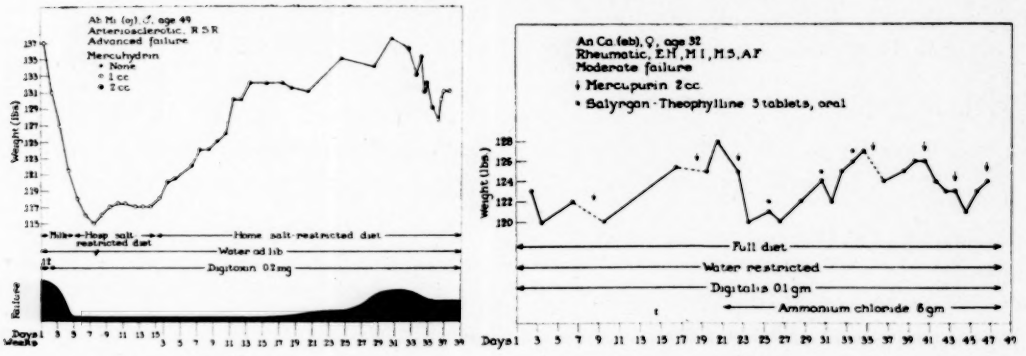


FIG. 12. Importance of the maintenance dose of the mercurial diuretic. Compare with Figure 11. Note the gradual rise of weight due to fluid, followed by symptoms of failure when the maintenance dose of the mercurial was interrupted.

FIG. 13. Type of response of congestive failure to current methods of treatment.

weight. On the contrary, it is precisely the object of the maintenance doses to maintain such a constant urine flow that the weight curve will tend to show only minimal fluctuations. If the doses are properly spaced, a daily water balance will be maintained at the optimum level. Under these conditions, the dose of the mercurial will serve its function without producing greater urine flow (as shown by the fall in weight) than was present on the previous day. An example may serve to clear the point: A physician used a daily dose of mercuhydrin in one of his patients until the weight declined from 150 to 135 pounds. Symptoms and signs of failure subsided. When a few additional daily doses failed to reduce the weight below 135 pounds, he prolonged the interval between doses to every four days. As a result the body weight rose to 139 pounds before each injection and each injection produced a prompt loss of 4 to 5 pounds, giving rise to unpleasant symptoms, chiefly prostration. In this case, a reduction of the dose to 1 cc. and the interval to every two days resulted in a constant weight of 135 pounds with negligible fluctuation and the prostration after each dose vanished. Again, there is the similarity between the problem of insulin in diabetes and the mercurial in congestive failure. In diabetes, it is not considered proper therapy to allow the patient to develop glycosuria, ketonuria and symptoms and then attempt to abolish them periodically by a dose of insulin. The plan for insulin is so worked out as to maintain the patient free of symptoms, free of ketonuria and free of glycosuria (or at a

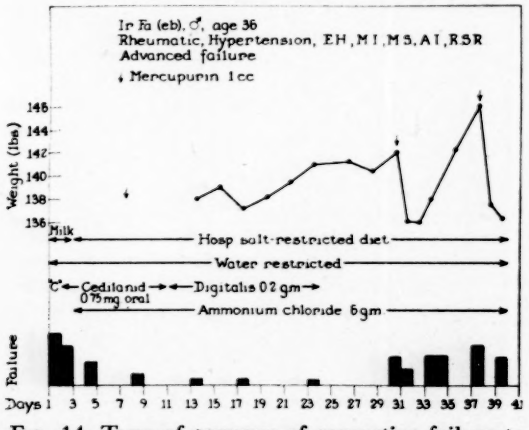


FIG. 14. Type of response of congestive failure to current methods of treatment.

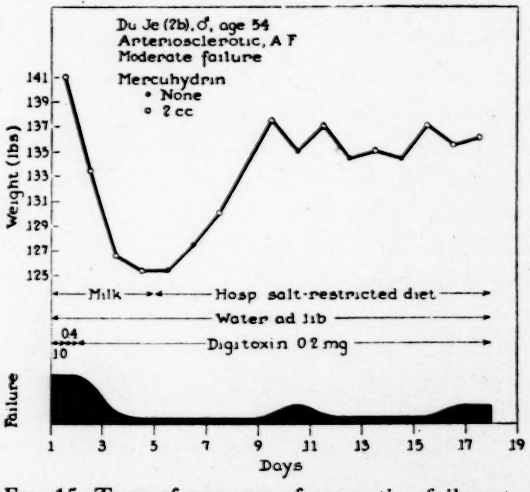
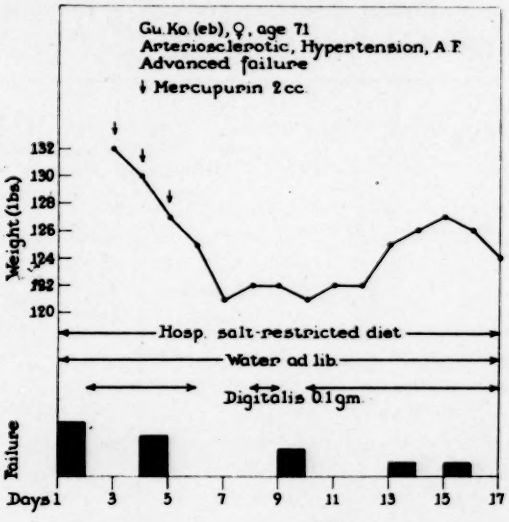


FIG. 15. Type of response of congestive failure to current methods of treatment.

level of a constant moderate glycosuria). This now is the plan we advocate for the control of congestive failure, namely, the adjustment of the dose of the mercurial as well as the interval between doses in order to maintain a constant body weight after the optimum state has been established.

failure. They are mentioned more particularly in order to point out that if the proposed regimen is carried out with due regard to adjustments in dosage of drugs, water intake and salt restriction required by individual cases, the course of the treatment progresses uneventfully. There was no in-



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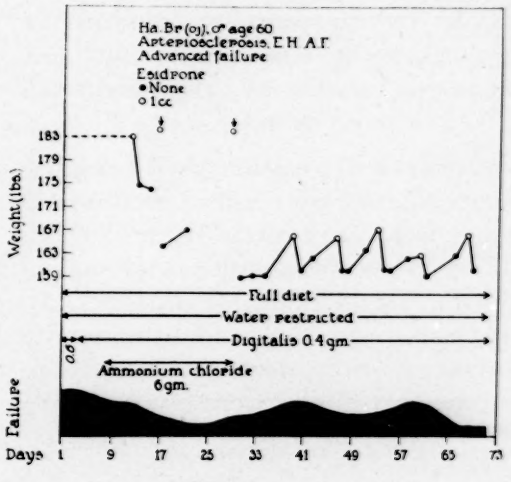

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FIG. 16. Type of response of congestive failure to current methods of treatment.
FIG. 17. Type of response of congestive failure to current methods of treatment.

Frequent injections often create a problem if a physician is necessary for all of them. We strongly urge, therefore, that a member of the family and sometimes the patient himself be instructed in the simple technic of an intramuscular injection after the physician has succeeded in establishing the proper maintenance program. The physician may then make periodic checks in order to determine any revision in the system which may become necessary.

Unpleasant Symptoms. An attempt was made to ascertain the nature of the unpleasant symptoms which might be ascribed to the proposed regimen in the 140 admissions so treated. There were such complaints as hunger, weakness, muscular cramps (six cases), nausea and vomiting (three cases), headache, dizziness, diarrhea (three cases) and constipation. It is difficult to be certain of the rôle of the treatment in causing any of these symptoms since these patients were all very ill and such symptoms are common in patients with advanced

stance of symptoms sufficiently disturbing to necessitate the interruption of treatment. There was no instance of the cerebral disturbances which have been described in relation to vigorous and excessive dehydration.[33,34] At this point it is well to re-emphasize the fact that, while dehydration constitutes a conspicuous part of the plan of treatment, the details of its application take sufficient cognizance of the danger of excessive dehydration to insure against its occurrence.

Fatal Cases. Among the group of 133 patients described in the next section, who were treated by the proposed regimen, there were twelve deaths. The difficulties in determining the precise cause of death in patients with advanced congestive failure are well known. The numbers were not sufficient for a statistical comparison of causes of death in cases treated by this method with those treated by other methods. It seemed desirable, however, to present a brief summary of the course in these cases

to document our belief that the fatalities were of the same general variety known to occur in similar groups of patients treated by any method. They included active rheumatic carditis, renal failure, coronary thrombosis, cerebral vascular accidents, bronchopneumonia, a reaction to a bronchogram and unresponsive congestive failure.

COMPARISON OF RESULTS IN CONGESTIVE FAILURE TREATED BY THE CURRENT ROUTINE METHODS WITH THOSE BY THE PROPOSED METHOD

The records of 376 patients with cognestive failure treated by routine methods in current use were examined. These methods (Figs. 12 to 17) varied considerably but all involved the use of digitalis, diuretics, attempts at salt restriction and attention to water intake. Various preparations of digitalis were employed and were given usually in divided doses, often taking several days for digitalization. Considerable dependence was placed on oral diuretics and mercurial diuretics were usually given at infrequent and irregular intervals. Frequently, diuretics were employed only after response to other measures had not proved sufficiently fruitful. Salt restriction was attempted by a variety of dietary adjustments; it was rarely systematic and was usually without adequate provisions for further reduction in the salt intake if the response proved inadequate. Water was commonly restricted. A chart of the body weight was not commonly used as the guide; the course was usually followed by changes in subjective symptoms and by inspection of gross and visible edema. The mercurial diuretics played little part in the plans for maintenance.

As seen in Table 1, these patients had a total of 502 admissions. About three-fourths were admissions during the past ten years and about one-half in the past five years. The practice in four hospitals in New York is represented, one a large municipal hospital and three large voluntary hospitals. In the entire group of patients with congestive failure, an average of 23.6 days elapsed from the day of admission to discharge, varying from nineteen to thirty days in the different hospitals.

The records were examined for all information relating to the type of heart disease, degree of failure, signs of improvement and degrees of recovery. The degrees of failure were classified into three groups: "moderate," those with shortness of breath on exertion, little or no orthopnea, pulmonary râles, liver edge not more than two fingers below the right costal margin and moderate pretibial edema; "advanced," those showing the foregoing signs but with the liver edge more than three fingers below the right costal margin and advanced edema of the legs; "extreme," those showing the foregoing signs including hydrothorax or ascites and/or edema up to and including the abdominal wall. In patients with predominantly so-called "left heart failure," the "moderate" included those with orthopnea, pulmonary râles and paroxysms of dyspnea; the "extreme" included those with pulmonary edema. The degrees of recovery were also classified into three groups: those

TABLE 1

DURATION OF HOSPITALIZATION OF PATIENTS WITH CONGESTIVE FAILURE TREATED BY THE ROUTINE METHODS IN CURRENT USE

Hospital	Years	No. Records Reviewed		Duration of Hospital Stay of All Admissions	
		Admissions	Patients	Average (days)	Range (days)
Bellevue	1930–1947	179	121	19.0	2–137
Post-Graduate	1935–1946	67	52	25.8	2– 82
Beth Israel	1938–1946	119	94	20.1	1– 59
Joint Diseases	1930–1946	137	109	30.1	1–101
Totals		502	376	23.6	1–137
	1930–1937	150 (29.9%)			
	1938–1947	352 (70.1%)			
	1942–1947	231 (46.2%)			

TABLE II

RESULTS OF TREATMENT BY CURRENT ROUTINES IN 376 PATIENTS WITH CONGESTIVE FAILURE IN FOUR HOSPITALS

Etiology	No. Records Reviewed		Degree of Failure (Admissions)			Deaths among Patients	Degree of Recovery (Admissions)			Duration of Hospital Stay of All Admissions (days)	
	Admissions	Patients	Moderate	Advanced	Extreme		None or Very Slight	Moderate	Complete	Average	Range
			No. %	No. %	No. %	No. %	No. %	No. %	No. %		
Rheumatic	112	75	24 (21.4)	48 (42.9)	40 (35.7)	20 (26.7)	34 (30.4)	28 (25.0)	50 (44.6)	25.9	2–92
Arteriosclerotic	80	65	18 (22.5)	36 (45.0)	26 (32.5)	17 (26.2)	19 (23.8)	16 (20.0)	45 (56.3)	24.7	2–101
Hypertensive	287	218	76 (26.5)	129 (44.9)	82 (28.6)	50 (22.9)	77 (26.8)	72 (25.1)	138 (48.1)	22.8	1–137
Others	23	18	3 (13.0)	13 (56.5)	7 (30.4)	3 (16.7)	9 (39.1)	8 (34.8)	6 (26.1)	23.0	6–93
Totals	502	376	121 (24.1)	226 (45.0)	155 (30.9)	90 (23.9)	139 (27.7)	124 (24.7)	239 (47.6)	23.6	1–137

TABLE III

LENGTH OF TIME REQUIRED FOR RECOVERY IN 196 PATIENTS WITH CONGESTIVE FAILURE TREATED BY THE ROUTINE METHODS IN CURRENT USE

Etiology	No. Records Reviewed		Degree of Failure (Admissions)			Time Required for "Cure" of Failure (days)		Duration of Hospital Stay of All Admissions (days)	
	Admissions	Patients	Moderate	Advanced	Extreme	Average	Range	Average	Range
			No. %	No. %	No. %				
Rheumatic	50	41	20 (40.0)	19 (38.0)	11 (22.0)	20.7	4–68	27.7	6–92
Arteriosclerotic	45	40	12 (26.7)	24 (53.3)	9 (20.0)	15.9	3–69	22.7	4–76
Hypertensive	138	108	60 (43.5)	51 (37.0)	27 (19.5)	12.7	3–33	20.8	3–133
Others	6	6	1 (16.7)	4 (66.7)	1 (16.7)	22.7	4–34	27.8	11–39
Totals	239	196	93 (38.9)	98 (41.0)	48 (20.1)	15.1	3–69	22.8	3–133

TABLE IV

RESULTS OF TREATMENT BY THE PROPOSED REGIMEN IN 133 PATIENTS WITH CONGESTIVE FAILURE

Etiology	No. Admissions	No. Patients	Degree of Failure (Admissions)			Deaths (Patients)	Degree of Recovery (Admissions)			Duration of Hospital Stay (days)	
			Moderate	Advanced	Extreme		None or Very Slight	Moderate	Complete	Average	Range
			No. %	No. %	No. %	No. %	No. %	No. %	No. %		
Rheumatic	31	28	0	15 (48.4)	16 (56.1)	2 (7.1)	1 (3.2)	0	30 (96.8)	16.2	4–34
Arteriosclerotic	44	42	4 (9.1)	16 (36.4)	24 (54.5)	2 (4.8)	0	6 (13.6)	38 (86.4)	12.5	5–30
Hypertensive	55	54	4 (7.3)	22 (40.0)	29 (52.7)	6 (11.1)	2 (3.6)	3 (5.5)	50 (90.9)	13.3	4–30
Others	10	9	0	2 (20.0)	8 (80.0)	2 (22.2)	0	2 (20.0)	8 (80.0)	16.0	5–30
Totals	140	133	8 (5.7)	55 (39.3)	77 (55.0)	12 (9.0)	3 (2.2)	11 (7.8)	126 (90.0)	13.7	4–34

in whom improvement was absent or negligible; "moderate," those in whom considerable relief of symptoms and edema had resulted although there still remained some gross edema and pulmonary râles; "complete," those in whom all symptoms of failure and signs of edema had vanished although enlargement of the liver persisted, a change which is frequently permanent in patients with long standing congestive failure. These have been summarized in Table II. All the common forms of heart disease are represented. About three-fourths of them were in at least "advanced" failure. Nearly one-fourth of them died and somewhat less than 50 per cent were discharged with recovery substantially complete.

In the case of those in whom recovery was "complete," a close approximation was made in arriving at the period from the time of admission to the disappearance of signs and symptoms. In comparing the two methods of treatment in the patients with "complete" recovery, the time it takes to bring it about has more meaning than the duration of hospital stay since the latter is often influenced by factors which have nothing to do with the treatment. Table III summarizes the results of treatment with the current methods in 196 patients (239 admissions) in whom the recovery was "complete." It took an average of about fifteen days, varying from about thirteen to twenty-three days, in the different types of heart disease.

Table IV summarizes the results with the proposed method of treatment in 133 patients (140 admissions) with congestive failure. About 94 per cent of the admissions were in at least "advanced" failure. Only 9 per cent of the patients died and in 90 per cent of admissions recovery was "complete."

Table V summarizes the results in 119 patients (126 admissions) treated by the proposed regimen in whom recovery was "complete." It took an average of about six days from the day of admission to the disappearance of signs and symptoms of failure.

It may be seen from Tables III and V that for the two methods of treatment there were a similar number of admissions of hypertensive heart disease with failure in the most extreme degree in which recovery was "complete" (twenty-seven and twenty-six cases, respectively). These were examined for the time required for "recovery." The average for the current methods was 17.6 days (7–33); for the proposed method, 8 days (3–18).

Since, as seen in Table III, rheumatic patients in failure tend to take longer to recover than hypertensive patients and since

TABLE V

LENGTH OF TIME REQUIRED FOR RECOVERY IN 119 PATIENTS WITH CONGESTIVE FAILURE TREATED BY THE PROPOSED REGIMEN

Etiology	No. Admissions	No. Patients	Degree of Failure (Admissions)			Time Required for "Cure" of Failure (days)		Duration of Hospital Stay of All Admissions (days)	
			Moderate	Advanced	Extreme				
			No. %	No. %	No. %	Average	Range	Average	Range
Rheumatic	30	27	0	15 (50.0)	15 (50.0)	6.5	3–14	16.4	4–34
Arteriosclerotic	38	36	4 (10.5)	16 (42.1)	18 (47.4)	5.8	2–14	7.3	5–30
Hypertensive	50	49	4 (8.0)	20 (40.0)	26 (52.0)	6.5	3–18	12.7	4–30
Others	8	7	0	2 (25.0)	6 (75.0)	5.5	2– 8	14.5	5–30
Totals	126	119	8 (6.3)	53 (42.1)	65 (51.6)	6.2	2–18	12.1	4–34

the degree of failure might be expected to influence the time for recovery, it was necessary to ascertain whether or not the groups treated by the two methods were comparable with respect to these points. The characteristics of the two groups are assembled in Table VI. It may be noted that they are substantially similar with respect to etiology, sex, and age. In regard to the severity of the failure, the group treated by the proposed method had a higher incidence of the more severe grades of failure.

TABLE VI
CHARACTERISTICS OF THE PATIENTS WITH CONGESTIVE FAILURE USED IN THIS STUDY

Characteristics	Treated by Current Methods	Treated by the Proposed Regimen
Etiology (No. and per cent of patients)		
Rheumatic	75 (19.9%)	28 (21.1%)
Arteriosclerotic	65 (17.3%)	42 (32.3%)
Hypertensive	218 (58.0%)	54 (40.6%)
Others	18 (4.8%)	9 (6.9%)
Total	376	133
Males		
No. and per cent of patients	223 (59.3%)	89 (66.9%)
Females		
No. and per cent of patients	153 (40.7%)	44 (33.1%)
Age		
Average	50.8	57.0
Range	7–81	20–83
Degree of failure (No. and per cent of admissions)		
Moderate	121 (24.1%)	8 (5.7%)
Advanced	226 (45.0%)	55 (39.3%)
Extreme	155 (30.9%)	77 (55.0%)
Total	502	140

It is well known that patients with predominantly so-called "left heart failure" often become free of symptoms rapidly after being put at rest, much more so than in those who also have a large element of so-called "right heart failure" with massive edema and ascites. In Table VII, the two groups are compared with regard to the different types of congestive failure. It may be noted that the two groups are practically identical with respect to the representation of the two types of congestive failure.

The essential results by the two methods of treatment are summarized in Table VIII. The term "maximum results" used in this table has a fairly precise meaning for those patients treated by the proposed method. It was taken as the point at which signs and symptoms of failure subsided and the body weight reached a resistant level or the point at which the course of treatment seemed to produce no further improvement. However, in many of the patients treated by the prevailing methods, the decision concerning "maximum improvement" presented considerable difficulty, since their course so often represented an endless succession of advances and regressions which, after the

TABLE VII
LENGTH OF TIME REQUIRED FOR RECOVERY IN DIFFERENT TYPES OF CONGESTIVE FAILURE

	Treated by Current Routine Methods	Treated by the Proposed Regimen
No. patients	196	119
No. admissions	239	126
"Left cases" (predominantly "left failure") (No. and per cent admissions)	49 (20.5%)	23 (18.3%)
"Right cases" ("right failure" with varying degrees of "left failure") (No. and per cent admissions)	190 (79.5%)	103 (81.7%)
Days to recovery in "left cases"	10.8	4.3
Days to recovery in "right cases"	16.2	6.6
No. and per cent "left cases" in the etiologic groups		
Rheumatic	15 (30%)	3 (10%)
Arteriosclerotic	8 (17.8%)	8 (21.1%)
Hypertensive	25 (18.1%)	9 (18%)
Other	1 (16.7%)	3 (27.5%)
No. and per cent "right cases" in the etiologic groups		
Rheumatic	35 (70%)	27 (90%)
Arteriosclerotic	37 (82.2%)	30 (78.9%)
Hypertensive	113 (81.9%)	41 (82%)
Other	5 (83.3%)	5 (82.5%)

patient had lingered in bed for a period of 30 or 40 days, seemed to have been terminated quite arbitrarily by a sense of futility. (Figs. 13, 14 and 17.) It may be seen that in two substantially similar groups of patients, the results with the current methods of

TABLE VIII
RESULTS IN CONGESTIVE FAILURE TREATED BY CURRENT METHODS COMPARED WITH THOSE BY THE PROPOSED REGIMEN

	Treated by the Current Methods	Treated by the Proposed Regimen
No. admissions	502	140
No. patients	376	133
Males	59.3%	66.9%
Females	40.7%	33.1%
Average age (and range)	50.8 (7–81) yr.	57.0 (20–83) yr.
Etiology (per cent patients)		
Rheumatic	19.9%	21.1%
Arteriosclerotic	17.3%	32.3%
Hypertensive	58.0%	40.6%
Other	4.8%	6.9%
Degree of congestive failure (Per cent admissions)		
Moderate	24.1%	5.7%
Advanced	45.0%	39.3%
Extreme	30.9%	55.0%
Deaths (per cent patients)	23.9%	9.0%
Degree of recovery (Per cent admissions)		
None or slight	27.7%	2.2%
Moderate	24.7%	7.8%
Complete	47.6%	90.0%
Weight loss in admissions with complete recovery (average and range)	*16.4 (2–41) lb.	*15.6 (2–55) lb.
Duration of hospital stay (All admissions—average and range)	23.6 (1–137) days	13.7 (4–34) days
Average time to maximum improvement	†19.6 days	†6.4 days
Time to recovery (In those who recovered completely—average and range)	15.1 (3–69) days	6.2 (2–18) days

* Sufficient weighings to be used as a guide were made in only 95 of the 239, and 122 of the 126 admissions, with complete recovery.

† Based on 419 admissions in the case of the current methods, and 134 in the case of the proposed method. They include deaths (seven and six cases, respectively, in the two groups) in which improvement of failure resulted although patients subsequently died of one or another cause.

treatment show 47.6 per cent "complete" recoveries, 23.9 per cent deaths, an average of 19.6 days for the maximum results yielded by the particular treatment in all admissions and an average of 15.1 days required for "complete" recovery; while the results with the proposed method of treatment show 90 per cent "complete" recoveries, 9 per cent deaths, an average of 6.4 days for maximum results obtained in all admissions and an average of 6.2 days required for "complete" recovery.

COMMENT

This study has placed agents for dehydration (the mercurial diuretic and salt restriction) in the first rank among measures effective in the control of congestive failure. How does this accord with the prevailing views regarding the mechanism of congestive failure?

There have been many important reviews of the mechanism of congestive failure. A very informative analysis of the literature was recently published by Ellis.[35] There is now considerable resistance to the idea that the symptoms of congestive failure are the direct mechanical consequence of a diminished circulation.[36,37] It is clear that the term congestive failure, as applied to a clinical state, may embrace different physiologic abnormalities in different cases and in different stages.

Ellis restated the prevailing view that weakness of the contractile force of the heart muscle initiates the train of events although he points out that secondary factors may outweigh the importance of the initial cause. The formulation of congestive failure on the basis of primary muscle weakness has buttressed the common practice of placing digitalis first among the remedies for congestive failure because of its power to increase the contractile force of the failing heart muscle.[38] This notion has become so firmly fixed that it has tended to obscure the magnitude of the clinical problem of congestive failure in which digitalis seems to exercise little or no beneficial influence.

The chief types of cases in which the effect of digitalis is negligible or limited might be mentioned: There is the congestive failure in the course of active rheumatic carditis in which little tendency to control results from digitalis, such patients often advancing to pronounced edema while fully digitalized. There are the cases of mitral stenosis in which the sole symptoms and signs of congestive failure are shortness of breath, pulmonary râles or attacks of pulmonary edema. Digitalis is usually of little or no benefit in these. There is the large group of

patients with arteriosclerotic and hypertensive disease subject to dyspnea on exertion, orthopnea or attacks of pulmonary edema without signs of systemic congestion of "right heart failure." A very considerable proportion of these show little or no improvement with the digitalis glycosides. As a group, patients with difficulty predominantly on the pulmonary side ("left heart failure") do not respond nearly as well as those with the chief trouble in the systemic circuit ("right heart failure"). There is the long-standing controversy concerning the value of digitalis in congestive failure with sinus rhythm. Sir Thomas Lewis[39] considered it of importance only in auricular fibrillation. Luten[40] and Marvin[41] were among those who early showed it to be of substantial value also in cases with sinus rhythm. This has been amply confirmed, but the fact remains that as a group, those with sinus rhythm do not respond to digitalis nearly as well as those with auricular fibrillation; and the number of patients with congestive failure and sinus rhythm in whom digitalis exerts no conspicuous effect is quite impressive. Then there is the group of cases of congestive failure, long effectively maintained by digitalis alone, who, in advanced stages, also require the diuretic to enable them to carry on.

The point that must be stressed is the fact that diuretic agents are not only helpful in accelerating recovery in cases in which digitalis alone may suffice after a more protracted course but that these agents alone, when effectively applied, control the congestive failure in a large proportion of those types of cases in which digitalis produces little or no benefits. We have numbers of patients with mitral stenosis and evidence of advanced pulmonary congestion (pulmonary râles, fluoroscopic signs) without systemic congestion in whom dyspnea, orthopnea and attacks of pulmonary edema are entirely uninfluenced by digitalis but in whom these symptoms and signs are brought under a high degree of control by an effective system of dehydration which maintains the patient in the state we have described as the "dry weight." The same is true, perhaps to an even more striking degree, in patients with hypertensive disease. Many of these patients, even when fully digitalized, suffer with frequent attacks of nocturnal dyspnea or pulmonary edema; these often vanish on a system of diuretic measures which effectively establish and maintain the "dry weight." In children with congestive failure resulting from active carditis, the edema often has a renal distribution. It has been pointed out in the literature[42] that the diuretics are very effective in these and that in many of such cases in which digitalis is of little or no benefit the symptoms and the edema may be brought under control by the use of a potent diuretic.[43]

It may be well to mention at this point a common source of misunderstanding. Physicians are accustomed to apply the term congestive failure only to those patients with pitting edema of the legs or enlargement of the liver or pulmonary râles. We have encountered resistance to the idea of using diuretic agents in the absence of these signs on the grounds that there was no evidence of congestive failure. It should be remembered that the extracellular fluid may increase to 50 per cent above normal before pitting of the legs occurs[44] and that the presence of pulmonary râles depends on the location of the fluid in the lungs;[45] there are râles if the edema fluid is intra-alveolar but there may be none if the fluid is interstitial. Many patients in congestive failure with an extreme sense of suffocation do not show any pulmonary râles. A typical case of this kind is shown in Figure 18. The patient, a physician, was sixty-one years old. He had hypertensive and arteriosclerotic heart disease for many years and had developed massive enlargement of the heart. Two years ago, he began to suffer with shortness of breath on exertion. This increased progressively until orthopnea and paroxysmal dyspnea appeared. In the past eight months, he was completely incapacitated; he was barely able to lie down without a sense of suffocation; he was subject to paroxysms of dyspnea even while sitting in bed or in a chair. A course of treatment in the hospital

failed to bring about any improvement. This treatment consisted of intensive digitalization, several doses of papaverine daily and sedation. A dose of ¼ gr. of morphine resulted in profound depression with Cheyne-Stokes respiration. An intravenous

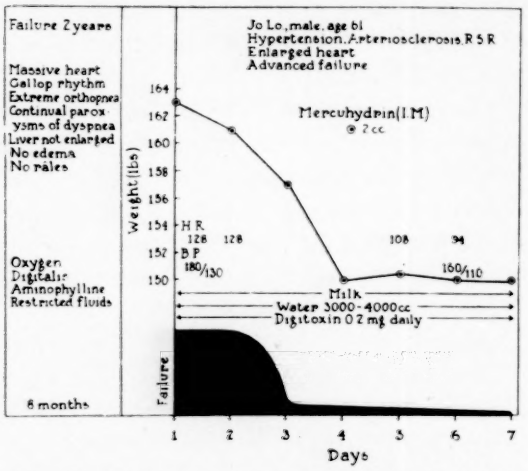

FIG. 18. Typical response of congestive failure to the proposed regimen. Note the fact that extreme respiratory distress existed and was promptly relieved with the loss of 10 pounds of fluid in a patient in whom there were none of the usual signs of congestive failure (no râles, no edema of the legs and no enlargement of the liver).

injection of aminophylline was used once or twice a day since it seemed to relieve the respiratory distress for a period of four or five hours. His physician labeled his diet "salt-free" but it turned out to be a regular diet in which salt was used freely in the cooking; however, salt was withheld from the tray. Emphasis was placed on the restriction of water and the patient frequently took pains to avoid an intake of more than 500 cc. a day. Matters went from bad to worse and at the time the revised treatment was applied all hope for recovery had been abandoned. The patient was readmitted to the hospital. The blood urea nitrogen at this time was 27 mg. The patient was placed on a diet consisting of six glasses of milk daily and a daily water intake of between 3,000 and 4,000 cc. A long discussion in more than one session was necessary to shake his conviction that so much water would do harm. In addition, he received a daily intramuscular injection of 2 cc. of mercuhydrin. Within four days, the patient lost a total of 10 pounds of body weight; the blood urea nitrogen was 26 mg. at this time. The relief of symptoms was dramatic; dyspnea and orthopnea vanished and on the sixth day the patient was discharged from the hospital with a maintenance system of treatment to be carried on at home. It should be re-emphasized that the need for a course of dehydration had not been suspected by his physician because the patient presented none of the usual signs of edema; the lungs were clear; there were no pulmonary râles; there was no pitting edema of the legs and there was no enlargement of the liver.

If it is a fact that heart muscle weakness initiates the train of events in congestive failure, the absence of therapeutic response to digitalis in so many suggests the possibility that there may be different types of muscular failure, some of which are and some are not reversed by digitalis. In our studies with the papillary muscle,[46] we encountered some preparations in which the glycosides did not succeed in enhancing the systolic force. The conditions determining a positive response are unknown although it was observed that failures were more frequent with the muscle in serum than in Ringer's solution.

It may be noted, however, that what initiates the train of events may be of only limited importance from the practical standpoint. The case of acute coronary thrombosis may serve to illustrate the point. The initial injury to the contractile power of the heart is promptly followed by a profound slowing of the circulation and fall of the systemic pressure, a state of peripheral circulatory shock. It begins as an acute failure of the heart but shock soon takes over, and the therapeutic problem is often best met by the treatment of the shock, not that of the primary muscle failure of the heart which initiated it.

In a broader sense, heart muscle weakness can be viewed only as one of the links in a complex chain of causation; there are antecedent factors in heart disease, possibly chemical, which give rise to the muscle weakness and the latter in turn (as well as other factors) may give rise to a disturbance

which is the immediate cause of the signs and symptoms of the clinical state, known as congestive failure. The evidence is becoming increasingly convincing that the immediate cause is a disorder in salt and water metabolism leading to tissue hyperhydration. The disturbance in electrolyte balance in heart disease, the existence of which was noted nearly fifty years ago,[47] has received special attention in recent years. Futcher and Schroeder[25] found that patients with chronic heart disease (recovering from congestive failure) have a markedly diminished capacity to excrete salt, 30 per cent of the normal or less, and indicated that it may be due to an increased renal reabsorption of salt. The studies of Warren and Stead[48] and of Merrill[49] have emphasized the renal factor in the retention of salt in patients with congestive failure. Further light has been thrown on this subject by the very interesting work of Reaser and Burch[50] with radioactive sodium. Not only is salt retained by patients in congestive failure but excessive salt administration may precipitate the typical signs and symptoms of congestive failure in patients with heart disease[2] as well as in some without heart disease.[51] It is also noteworthy that hypertension, a condition which most commonly gives rise to congestive failure, involves a disturbance in the behavior of salt, a resistance to salt loss when the patients are placed on a highly restricted salt intake[52] and marked lowering of blood pressure in some of these patients when they are placed on a diet of extremely low salt content.[53]

From the theoretical standpoint, the clinical syndrome of congestive failure may be defined in terms of a disturbance occurring either at the level of heart muscle contraction or at the level of the electrolyte imbalance or a disturbance at any other level which may represent a link in the chain of causes. However, from the practical standpoint it would seem appropriate to define the clinical syndrome in terms of the link in the chain of causation which is most accessible to attack and at which point it can be most regularly interrupted. Accordingly, congestive failure may be formulated as a clinical state involving a disturbance in salt and water metabolism leading to tissue hyperhydration, occurring most commonly in chronic heart disease and resulting usually from a chronic circulatory disorder in the pulmonary or systemic circuit.

The foregoing observations, we believe, lend support to the position that the sequence employed in the most common practice of trying digitalis first and then adding a diuretic, if necessary, is in need of revision. In the concept of treatment, the indications are that the order should be reversed; an effective technic for dehydration with salt restriction, free supply of water and a potent diuretic become the base of the system; digitalization becomes an auxiliary or accessory measure, without value in many but of some use in others, and essential in a certain group, especially those with auricular fibrillation.[54] From the standpoint of results, this seems to be a more fruitful approach; there is indication that the incidence of improvement in congestive failure may be much higher from an effective system of dehydration alone than from digitalis alone.[50] Since there is no satisfactory way of distinguishing the two types of cases and since there is considerable overlapping, that is, patients who do better when receiving both measures, it is advocated for the present that both be used simultaneously in a routine manner until proof appears in a particular case that it is feasible to dispense with one or the other.

SUMMARY AND CONCLUSIONS

In this report a method is described for the routine treatment of congestive failure which brings the problem of congestive failure under a degree of control which has not been secured with any of the methods in general routine use.

It is pointed out that heart muscle weakness represents only one of the links in a complex chain of causation of the clinical state of congestive failure and that another link, namely, that of a metabolic disturbance involving salt and water retention, constitutes a more important one from the

therapeutic standpoint. In this system diuretic agents are the primary factors and digitalis plays a secondary rôle.

The proposed method is applicable not only to patients with advanced failure with pitting edema, enlarged liver, pulmonary râles and effusions but to the large group of cardiac patients with only shortness of breath on exertion, orthopnea, attacks of cardiac asthma, or pulmonary edema, and to a proportion of patients in whom the presenting symptoms of failure are paroxysms of disordered rhythm or attacks of cardiac pain. It provides relief for the large group of cardiac patients in whom digitalis is of little or no benefit.

The regimen is easily applied both in the hospital and in the home. It requires a minimum of nursing and medical supervision. It involves five cardinal factors: the simultaneous use of the mercurial diuretics, salt restriction, abundant water, digitoxin and the charting of the course by a record of the body weight. The measures are arranged in a system which provides the most effective results most quickly in the largest number. The secret of success lies in the way these measures are combined and applied.

It provides not only for abolishing the signs and symptoms of failure but for the maintenance of the gains. The same five cardinal factors used in abolishing an attack are also employed in the system for maintenance to prevent the recurrence of congestive failure.

The present study, comparing the results in 502 admissions for congestive failure (representing a cross section of the current practice in New York City) with the results in 140 similar admissions treated by the proposed system, shows that the symptoms and signs of congestive failure subside in about 90 per cent of hospital admissions, when this system is employed routinely, as against about 50 per cent with the current methods in common use; and the duration of required hospital stay is reduced to about one-third of the time necessary to bring about similar results by the current methods of treatment. The provisions for maintenance greatly reduce the high incidence of multiple hospital admissions occurring with the prevailing treatment. Broadly speaking, only two types of results are obtained with the proposed method, namely, a few failures and the rest complete recoveries. A third class, representing about one-third of the patients treated by other routines, namely, those with only moderate improvement, has practically vanished.

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CASE REPORTS OF PATIENTS WHO WERE TREATED BY THE PROPOSED REGIMEN AND WHO DIED

CASE 1. Patient Ri. Ab., a male, thirty-six years old, had rheumatic heart disease with enlarged heart, mitral stenosis and insufficiency, aortic stenosis and insufficiency, tricuspid insufficiency, normal sinus rhythm, advanced congestive failure and active rheumatic carditis. He was admitted with a temperature of 102°F. The routine regimen was applied. Symptoms and

signs of failure subsided after six daily doses of 2 cc. mercuhydrin; there was a loss of 11 pounds. The blood N.P.N. values during this week were 37, 25 and 30 mg. per 100 cc. In the next ten days, he received a total of four similar injections. On the thirteenth day of admission, he developed paroxysms of auricular fibrillation with heart rates as high as 160 a minute, with cough, blood-tinged sputum and severe dyspnea. The temperature during this time was as high as 101.4°F. Attempts to control the symptoms and fibrillation by means of oxygen and quinidine were unsuccessful and the patient was found dead in the early hours of the morning of the seventeenth day.

Comment: Death was probably due to active rheumatic carditis, after satisfactory initial response to therapy.

CASE II. Patient He. Ok., a male, forty years old, had syphilis, rheumatic heart disease with enlarged heart, aortic insufficiency, mitral insufficiency, normal sinus rhythm, extreme congestive failure and possible active rheumatic carditis. The patient was nearly moribund on admission. The routine regimen was applied. The urine output was 500 cc. on day of admission, and continued essentially unchanged during treatment which included 2 cc. mercuhydrin every twelve hours. There was no response and the patient expired on the fourth day.

Comment: Death was due to congestive failure with possible active rheumatic carditis, without response to therapy.

CASE III. Patient Le. Wa., a male, sixty years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, advanced congestive failure and pulmonary emphysema. He had received three doses of a mercurial weekly for six months. The routine regimen was applied. Symptoms of failure disappeared after five daily doses of 2 cc. of the mercurial; there was a loss of 9 pounds. No more doses of the mercurial were given. On the seventh day, the patient developed abdominal cramps, diarrhea and vomiting and symptoms progressed to coma, collapse and death on the fourteenth day. There was a clinical diagnosis of uremia. Laboratory data on the eleventh day: blood proteins 5.7 per cent; N.P.N. 129 mg. per 100 cc.; CO_2 combining power 22 vols. per cent. Postmortem report: primary contracted kidney; no lesions in gastrointestinal tract to account for symptoms; opinion of pathologist: kidney lesion not due to mercury.

Comment: Death was due to uremia of primary contracted kidney after satisfactory initial response to therapy.

CASE IV. Patient Ad. Ba., a female, sixty-one years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, auricular fibrillation, extreme congestive failure, extreme emaciation (weight 114 pounds., hemoglobin 8.5 Gm., red blood cells 2.9 million) and the specific gravity of urine was fixed between 1006 and 1010. The routine regimen was applied. Symptoms of failure subsided after six daily doses of 2 cc. mercuhydrin; there was a loss of 22 pounds. In the next eleven days 4 doses of 1 cc. mercuhydrin were administered. Being a case treated on another service, a daily dose of 6 Gm. ammonium chloride was used throughout the course, and water intake was not supervised and was low. On the fourteenth day, the patient developed drowsiness. Although free of congestive failure, her condition deteriorated in spite of intravenous infusions and she died on the seventeenth day. The blood N.P.N. on admission was 67 mg. per 100 cc., 75 mg. on the seventh day, and 85 mg. on the thirteenth day. Postmortem report: primary contracted kidney and cerebral edema.

Comment: Death occurred because of renal failure due to primary contracted kidney after satisfactory initial response to therapy.

CASE V. Patient Sa. Br., a female, sixty-three years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, extreme congestive failure, hypertensive encephalopathy and was nearly moribund. The routine regimen was applied; there were fourteen daily doses of 2 cc. mercuhydrin. The gross edema which extended to the breasts showed some regression but total improvement was slight. A confusional state persisted and the patient died on the fourteenth day.

Comment: Death caused by advanced congestive failure and hypertensive encephalopathy which showed only slight response to therapy.

CASE VI. Patient Ab. Ax., a male, sixty-six years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, extreme congestive failure and possible acute coronary thrombosis. The routine regimen was applied. He received fourteen daily doses of 2 cc. mercuhydrin with slight response and thoracic pain persisted. Being a case treated on another service, a daily dose of 6 Gm. ammo-

nium chloride was used throughout the course, and water intake was not supervised and was low. The patient died suddenly on the morning of the fifteenth day. Blood N.P.N. on the thirteenth day was 63 mg. per 100 cc.

Comment: Death was probably due to acute coronary thrombosis or pulmonary infarction without response to therapy.

CASE VII. Patient Da. Ab., a male, sixty-nine years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, extreme congestive failure, diabetes, pulmonary emphysema and had suffered a cerebral vascular accident one year previously. The routine regimen was applied. Symptoms of failure subsided after five daily doses of 2 cc. mercuhydrin; there was a loss of 7.5 pounds. On the fifth day, he died suddenly while talking to another patient. Blood N.P.N. on the fifth day was 47 mg. per 100 cc.

Comment: Death was probably due to cerebral vascular accident, after satisfactory initial response to therapy.

CASE VIII. Patient Le. Sc., a female, eighty years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, auricular fibrillation, extreme congestive failure, parkinsonism and senile dementia (disoriented). The routine regimen was applied. Symptoms of failure diminished moderately after six doses of 2 cc. mercuhydrin in the first seven days; there was a loss of 15 pounds. No more doses of the mercurial were given. The patient was disoriented throughout the course and on the seventh day developed drowsiness and Cheyne-Stokes respiration after 2 Gm. chloral hydrate. There was a clinical diagnosis of cerebral vascular accident. The patient became stuporous; her temperature rose as high as 104°F. (possible pneumonia) and she expired on the ninth day. Blood N.P.N. on admission was 37 mg. per 100 cc., 64 mg. on the fourth day, 34 mg. on the seventh day and 80 mg. on the eighth day.

Comment: Death was probably due to cerebral vascular accident with terminal pneumonia in an aged person with advanced arteriosclerotic cerebral changes after moderate initial response to therapy.

CASE IX. Patient Sa. Ro., a male, sixty-three years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, extreme congestive failure and morphine addiction. The routine regimen was applied and he received twenty-one daily doses of 1 cc. mercuhydrin. Improvement was slight (lost 4.5 pounds in first three days). His course was progressively downward and he expired with symptoms of extreme failure and coma on the twenty-first day. Post mortem report: extensive pathologic changes, purulent pericarditis, consolidation of lower lobes of both lungs; advanced ulcerative and calcified lesions of the aorta, small contracted kidneys and massive cirrhotic liver.

Comment: Death was due to extreme congestive failure and bronchopneumonia with slight initial response to therapy.

CASE X. Patient Sa. Fe., a female, seventy years old, had arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, coronary thrombosis, extreme congestive failure and diabetes. The routine regimen was applied. Symptoms of failure subsided after eleven daily doses of 2 cc. mercuhydrin; there was a loss of 34 pounds. On the thirteenth day, the patient developed a severe attack of pain in the chest and left shoulder and died during sleep.

Comment: Death was probably due to acute coronary thrombosis or pulmonary infarction after complete recovery from congestive failure.

CASE XI. Patient Wa. Mc., a male, forty-three years old, had bronchial asthma, pulmonary emphysema, cor pulmonale, bronchiectasis, normal sinus rhythm and extreme congestive failure. The routine regimen was applied. Symptoms of failure subsided after seven daily doses of 2 cc. mercuhydrin; there was a loss of 30 pounds. In the next ten days, six doses of 2 cc. mercuhydrin were administered. Because of the severe respiratory symptoms, the patient received almost daily doses of aminophylline and remained in the hospital for bronchogram which was performed on the thirteenth day. On the following day, dyspnea became intense, coma developed and the patient died of respiratory failure on the sixteenth day although clear of congestive failure. Blood N.P.N. ranged from 21 to 33 mg. per 100 cc. Postmortem report: cor pulmonale, bilateral bronchiectasis with cavities, edema of brain and normal kidneys.

Comment: Death caused probably by reaction to bronchogram after satisfactory initial response to therapy.

CASE XII. Patient Ma. Be., a male, sixty-one years old, had pulmonary fibrosis and emphysema, cor pulmonale, normal sinus rhythm, extreme congestive failure (intense cyanosis with periodic lapses into coma). The routine regimen

was applied. Considerable relief of symptoms occurred after seven doses of 2 cc. mercuhydrin in the first eight days and 2 cc. every twelve hours during the subsequent eight days; there was a loss of 28 pounds. There were many temporary changes in cardiac rhythm during the course, paroxysms of bigeminy and auricular fibrillation. Blood N.P.N. on admission was 50 mg. per 100 cc., 74 mg. on the fifth day, 80 mg. on the sixth day, 53 mg. on the eighth day, 48 mg. on the tenth day, 38 mg. on the twelfth day, 49 mg. on the thirteenth day and 39 mg. on the fifteenth day. In the early hours of the seventeenth day the the patient was found dead in bed (seen awake, alert, and without complaints 30 minutes previously).

Comment: Death possibly was due to cerebral vascular accident after marked initial response to therapy.

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Oral Administration of Mercupurin Tablets in Ambulatory Patients with Chronic Congestive Heart Failure*

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THERE are many patients with chronic congestive heart failure who, in spite of adequate treatment with the usual drugs, dietary control and parenteral mercurial diuretics, do not do well and constitute an important therapeutic problem. Because the immediate response to mercurial injections in this group of patients is usually satisfactory, it seemed that the problem might be approached by the administration of mercurial diuretics in such a manner as to produce a more constant diuresis. Since daily injections of mercurials are not practical over a long period of time, we attempted to achieve this result by the oral administration of mercurial diuretics. The published reports on this method of treatment were not promising[1] except for those by Batterman et al.,[2,3] who suggested that the drug might be a useful adjunct in the treatment of chronic congestive heart failure.

The idea of giving mercupurin constantly to control chronic congestive failure or possibly to prevent recurrence, although not commonly practiced, is feasible and has been suggested by Gold;[4] oral administration of mercupurin tablets† instead of injections seemed more desirable and worthy of trial.

PLAN OF TREATMENT AND SELECTION OF PATIENTS

Patients were selected who had been under our own observation for a long period of time and who demonstrated chronic or recurrent congestive heart failure in spite of adequate treatment, including repeated injections of mercurial diuretics. Patients with impaired renal function were excluded. Our initial method of oral mercury treatment was experimental and included varying doses given in a variety of ways, as indicated below. Our aim was to find for each patient a method of administration and dosage of the mercupurin tablets which would relieve the signs and symptoms of congestive heart failure with minimal or no toxic reactions.

The preliminary methods of dosage and administration used were: (1) One tablet two or three times a day, or two tablets before breakfast for five consecutive days each week; (2) one to three tablets before breakfast every other day, or one to three tablets at bedtime every other evening; (3) five tablets before breakfast once or twice a week and (4) one to three tablets every morning before breakfast, or one tablet two or three times each day.

† Each tablet contains 120 mg. of mercupurin, which is equivalent to 30 mg. of mercury and 27 mg. of anhydrous theophylline, whereas 1 cc. of the parenteral solution contains 135 mg. of mercupurin. Mercupurin tablets were supplied by Campbell Products, Inc., New York, N. Y.

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The eleven patients investigated were ambulatory, had signs of gross congestive failure and were seen in the Cardiac Clinic at frequent intervals. In addition to oral mercupurin all patients were receiving digitalis and were on a low salt diet. All

TABLE I
PLAN OF ADMINISTRATION AND DOSAGE OF MERCUPURIN TABLETS

	Cases	Dosage
Daily	II, V and VIII	Three tablets each morning before breakfast
	VI	One tablet three times a day
Five consecutive days each week	I and IV	One tablet three times a day
	VII	Two tablets every morning before breakfast
Every other morning before breakfast	IX and X	Three tablets
Every other evening at bedtime	XI	Three tablets
	III	Two tablets

but one of the patients received ammonium chloride continuously.

As a result of our preliminary investigations the plan of treatment finally evolved consisted of hospitalizing those patients with signs of gross congestive heart failure who did not respond to oral therapy and of reinstituting oral therapy after all signs of failure disappeared. The plan of administration and dosage of mercupurin tablets found most effective was quite variable. (Table I.) No one of these plans in practice has proven uniformly superior. In treating a patient who tends to gain weight on an optimum regimen including acidifying salts, it has been our practice to initiate one of the four plans of treatment and change or modify it if toxic symptoms develop or if the symptoms and signs of congestive heart failure are not relieved. As soon as the most suitable plan was established, the patient followed it continuously.

When symptoms or signs of failure recurred under certain conditions (respiratory infections, paroxysmal rapid heart action, discontinuance of the tablets), one or two

TABLE II
DURATION OF ORAL MERCUPURIN MEDICATION

Cases	Duration in Months
I and IV	27
III	25
VII	20
IX	14
XI	12
VI	10
V	8
X	7
II	4½
VIII	3

doses of mercurial diuretic were given parenterally at weekly intervals, with continuance of the oral tablets.

At each visit the patient was given a supply of tablets sufficient to enable him to follow the prescribed plan of administration and dosage and was instructed not to deviate from this plan. At each visit the patient was questioned and examined for evidence of congestive heart failure and mercurialism. The patient's weight was recorded and the urine examined. In patients who showed albuminuria before the institution of the tablet regimen the blood non-protein nitrogen was determined at each visit.

RESULTS

The results were uniformly excellent and parenteral injections of mercurials were not necessary except as noted below. The patients have taken the mercupurin tablets for three to twenty-seven months (Table II).

Within one or two weeks after the institution of oral therapy, a loss of weight of 5 to 25 pounds was observed, following which the weight remained stationary.

The efficacy of treatment with mercupurin tablets was further shown by the effect of discontinuance of the treatment.

Cases I, IV, VII, IX and X developed signs and symptoms of congestive heart failure with increases in weight within three days to one week after the mercupurin tablets were omitted. With resumption of the mercupurin tablets and one or two doses of parenterally administered mercupurin, these patients became free of congestive failure and their weights returned to the previous stationary levels. In spite of the uninterrupted ingestion of the tablets, Cases I, IV and VI developed recurrence of signs and symptoms of congestive heart failure during respiratory infections. Case I required parenteral mercupurin while the oral tablets were continued; Case IV was hospitalized and Case VI regained his previous cardiac status with continuance of the oral mercupurin without the drug administered parenterally. Case I developed signs and symptoms of congestive failure after an episode of paroxysmal rapid heart action. With continued use of the mercupurin tablets and one parenteral dose of mercupurin she regained her former status.

Toxic Manifestations. Five patients (Cases IV, V, VIII, IX and X) on various dosage schedules have been free of toxic manifestations after taking the oral mercupurin from seven to twenty-seven months. Six others had toxic manifestations of one or several types.

Soreness of the abdomen without bowel symptoms was present in Case I on the days she took the tablets for a period of two months, one year after she began taking them. This complaint disappeared in spite of continued ingestion of the tablets. Anorexia and slight nausea, on the days Case XI ingested the tablets, developed five months after she began to take them and recurred for four months. These complaints disappeared after the time of administration was changed to the evening at bedtime. Abdominal cramps with or without diarrhea developed in Cases II, III, VI and VII. In Case II the cramps developed during the first week of ingestion of the tablets, disappeared in spite of the continued ingestion of the drug and failed to recur when the dosage of the drug was increased. In Case III two months after the oral tablet regimen was begun, increase of the dosage was accompanied by abdominal cramps and two to three bowel movements on the day following the ingestion of the tablets. Reduction of the dosage relieved the abdominal complaints. Case VI developed bloody stools and abdominal cramps for one day, three weeks after the ingestion of the tablets was begun. The tablets were omitted for several days with disappearance of the complaints. Two and three months after beginning the tablets he suffered with bouts of diarrhea and cramps, each lasting one day. These complaints disappeared in spite of the continued ingestion of the tablets. Eight months after beginning the tablets he suffered with diarrhea on three occasions, each lasting one day. These complaints disappeared although the tablets were continued. Case VII complained of abdominal cramps with one bowel movement a day during the second week after the ingestion of mercupurin tablets was begun. These complaints disappeared in spite of the continued use of the tablets. In the third week he developed anorexia, pain and itchiness of the gums. The tablets were then omitted for three weeks with disappearance of the complaints. Four and one-half months after the tablets were resumed he again complained of pain in his gums and teeth. The tablets were then omitted for six weeks, during which time the gums became normal except for residual pyorrhea. The tablets were then resumed for one year without recurrence of the gastrointestinal or gum difficulties.

Five patients (Cases I, II, III, IV and IX) showed no albumin in the urine throughout the study period. Six patients (Cases V, VI, VII, VIII, X and XI) had albuminuria before

the study was undertaken and continued to show varying amounts of albuminuria throughout the period of the study. Three patients (Cases I, II and III) with toxic gastrointestinal manifestations showed no albuminuria, while three patients (Cases VI, VII and XI) with albuminuria before and during the study developed toxic gastrointestinal symptoms and showed no increase in albuminuria.

Case II developed severe acute mercurialism after he had received oral mercupurin therapy for four and one-half months, during which time he was free of signs and symptoms of congestive heart failure and showed repeatedly negative urines. One week before the symptoms of mercurialism appeared a urine examination showed 4 plus albumin. Unfortunately, this finding was not reported promptly and the drug was continued an additional week at the end of which time the patient developed the picture of acute mercurialism with shock, renal insufficiency, hypochloremia, hypoproteinemia, anasarca and hypercholesterolemia. Symptoms of congestive heart failure were absent. Repeated attempts to raise the colloid osmotic pressure of the blood were unsuccessful and the patient expired one month after the onset of the acute symptoms.

COMMENTS

As pointed out by Batterman et al.,[2] although the immediate diuresis may not be great the effect of oral mercupurin may be more prolonged than that produced by the parenterally administered drug. Thus, patients who reaccumulate edema rapidly and require intravenous medication at frequent intervals may accumulate their edema at a much slower rate, or not at all, when given the oral medication. Constant diuresis appears to be maintained in those patients who have experienced relief of their congestive heart failure.

Gold[4] states that organic mercurials are usually eliminated completely, or almost so, in less than twenty-four hours and that a dose may be repeated every day with safety.

Regardless of the dosage and method of administration of the mercupurin tablets, toxic manifestations may occur. Such reactions do not usually limit the usefulness of the drug since they may not recur upon repeated or continued use of the tablets. Batterman et al.,[2,3] in their study of hospitalized and ambulatory patients on their multiple dose schedules, found that the latter group of patients was more prone to develop gastrointestinal irritation, the explanation for which was not found.

In the patients on a daily dosage of the tablets Batterman et al.,[3] found that the most common untoward reaction was digitalis toxicity in one-third of their ambulatory patients, which they believed was related to the phenomenon of mobilization of the digitalis from the edema fluid after diuresis was well established, i.e., after four to fourteen days of daily dosage when the existing edema was in the process of being removed. The signs of digitalis toxicity consisted in the development of auricular fibrillation, marked slowing of the ventricular rate in patients with auricular fibrillation and prolongation of A-V conduction time. Our patients showed none of these signs. Batterman et al.[3] believed that the symptoms of gastrointestinal irritation (anorexia, nausea, vomiting or diarrhea) that developed during the administration of mercupurin tablets were due to digitalis toxicity rather than to mercurial irritation, because these symptoms subsided completely when digitalis was discontinued or decreased, even though the oral mercupurin was administered uninterruptedly. They stated that "we have no doubt that true gastro-intestinal irritation caused by the daily dose of oral Mercupurin may be en-

countered, although it was not observed in our series of patients." Although we cannot definitely exclude digitalis intoxication in some of our patients with toxic manifestations, we found no clear evidence that such was the case. While the gastrointestinal symptoms of digitalis toxicity and mercurialism may be similar, we considered the cramps, diarrhea and bloody stools in our patients to be due to mercurialism.

Gingivitis was uncommon and when it appeared it subsided after oral mercupurin therapy was discontinued. Batterman et al.[3] observed that when the oral therapy was given a second time, two of their patients did not develop recurrence of the gingivitis. Our Case VII developed gingivitis on two occasions with subsidence each time after the drug was discontinued. After resumption of the oral mercupurin the gingivitis did not recur.

Increasing albuminuria with gastrointestinal symptoms in Batterman's patients occurred only in those with renal disease. Batterman et al.[3] allowed a rest period of one week to patients receiving daily dosage of mercupurin tablets after the maximum effect of diuresis had been achieved and this was repeated every month. In our patients rest periods were not instituted.

CASE REPORTS

CASE I. F. A., a seventy-one year old woman with hypertensive and coronary heart disease was hospitalized from February 7, 1944 to March 7, 1944, and from April 25, 1944 to May 7, 1944, for treatment of congestive heart failure. After discharge on May 7, 1944, she required intravenous or intramuscular injections of mercupurin at weekly intervals. When the interval between injections was two weeks, symptoms recurred in the second week. On November 30, 1944, she was started on one mercupurin tablet twice a day for five days a week. She did well until March 7, 1945, when she exhausted her supply of mercupurin tablets and promptly developed symptoms and signs of congestive heart failure. On March 22, 1945, she was given an intravenous injection of 2 cc. mercupurin and the mercupurin tablets were resumed; she again did well. In October and November, 1945, she experienced soreness of the abdomen without bowel symptoms when she took the mercupurin tablets. On January 1, 1946, she developed a grippal infection with recurrence of the congestive heart failure, in spite of the continued ingestion of the mercupurin tablets. On February 14, 1946 and February 21, 1946, she was given additional mercury in the form of intramuscular injections of 2 cc. mercupurin. On April 15, 1946, she suffered with an episode of rapid heart action of ten minutes' duration which was followed by the return of symptoms and signs of congestive heart failure. An intramuscular injection of 2 cc. mercupurin was given on April 25, 1946. The dosage of mercupurin was increased to one tablet three times a day for five days a week. Since then she has been free of congestive heart failure. Urine examinations have been repeatedly negative.

This case illustrates control of the signs and symptoms of congestive heart failure by orally administered mercupurin tablets. Exhaustion of the supply of the medication, a grippal infection and an episode of paroxysmal rapid heart action in spite of the continued ingestion of the tablets precipitated congestive heart failure and necessitated the temporary administration of mercupurin parenterally until the patient recovered her former reserve.

CASE II. L. B., a fifty-nine-year old man was hospitalized from January 6, 1944 to January 24, 1944, because of increasing effort dyspnea, nocturnal dyspnea and swelling of the ankles of five months' duration following myocardial infarction. The signs and symptoms of severe congestive heart failure disappeared after digitalization, two thoracenteses, four intramuscular mercupurin injections and a low salt diet with 6 Gm. NH_4Cl daily. He was hospitalized again from March 21, 1944 to April 7, 1944, with

congestive heart failure. Again, there was a good response to treatment and following his discharge from the hospital, he did fairly well with frequent intramuscular injections of mercupurin. Severe congestive heart failure recurred and he was again hospitalized in November, 1945. Following his discharge from the hospital, in spite of frequent injections of mercupurin and thoracenteses, the hydrothorax reappeared. On December 14, 1945, he developed a respiratory infection and on December 18, 1945, when the respiratory infection was clearing, he developed severe dyspnea which made necessary his readmission to the hospital on December 21, 1945 in a moribund state. The congestive heart failure responded promptly to therapy. Following his discharge from the hospital on January 13, 1946, he received intramuscular injections of mercupurin at intervals of two to three weeks, with relief of symptoms during the first week after the injection but with subsequent progressive development of signs and symptoms of congestive heart failure prior to the next injection. Mercupurin tablets, two every morning before breakfast, were started on September 6, 1946. On September 12, 1946, he felt well but on three occasions had abdominal cramps. The mercupurin tablets were continued without further cramps and on September 19, 1946, he reported that during the previous two days he experienced dyspnea on walking. The dosage of mercupurin tablets was increased to three every morning before breakfast.

He was free of signs and symptoms of congestive heart failure and showed repeatedly negative urines. On January 23, 1947, urine examination revealed 4 plus albumin. Unfortunately, this finding was not reported promptly and the drug was continued an additional week, at the end of which time the patient developed the picture of severe mercurialism. He was admitted to another hospital on February 4, 1947 in a state of shock. He developed renal insufficiency, hypochloremia, hypoproteinemia, anasarca and hypercholesterolemia; repeated attempts to increase the colloid osmotic pressure of the blood were unsuccessful. Symptoms of congestive heart failure were absent. He expired on March 7, 1947. Postmortem examination was not permitted.

The patient suffered severe recurrent congestive heart failure following acute myocardial infarction requiring repeated hospitalization, thoracenteses and mercurial injections. Complete relief was obtained with mercupurin tablets. Severe mercurialism developed and death occurred after one month.

Case III. S. B., a fifty-eight year old woman with mild hypertension, constrictive pericarditis and ascites was treated by intravenous injections of mercupurin at seven to ten day intervals beginning in May, 1942. On February 8, 1945, she was given one mercupurin tablet daily with negligible effect. Beginning February 15, 1945, she took two mercupurin tablets every other evening at bedtime, ammonium chloride, 4.0 Gm. during the day and digitalis. On April 12, 1945, because of ascites and slight leg and sacral edema the dose of mercupurin was increased for two weeks to three tablets every other evening at bedtime. During this period on the mornings following the ingestion of the tablets, she suffered with abdominal cramps and two to three daily bowel movements. The dose was reduced to two tablets every other evening with control of the ascites. At present, in spite of taking the mercupurin tablets at bedtime, she sleeps well and at 5:30 the following morning voids and continues to diurese all that day. Urine examinations have been repeatedly negative.

This was a patient with constrictive pericarditis, ascites and edema, requiring frequent intravenous injections of mercupurin, effectively controlled with mercupurin tablets.

Case IV. W. C., a fifty-four year old man with congestive heart failure and a history of myocardial infarction and hypertension, was treated with rest in bed, low salt regimen, digitalization, ammonium chloride and intravenous injections of mercupurin. Beginning October 7, 1943, weekly intravenous injections of mercupurin were necessary because of continuance of congestive heart failure. The results were unsatisfactory and on November 30, 1944, one mercupurin tablet twice a day for five days a

week was begun and after a week the dosage was increased to one tablet three times a day five days a week. Signs and symptoms of congestive heart failure disappeared but for purposes of study the plan of administration was changed to five tablets before breakfast twice a week and beginning on January 20, 1945 to five tablets once a week. Through February 10, 1945, the volume of urine after five tablets was approximately 2 quarts, less than after the intravenous administration of the drug. On February 11, 1945, he contracted a severe respiratory infection with abrupt development of congestive heart failure, requiring admission to another hospital for one month where he received intravenous injections of mercupurin every other day. He then continued the weekly ingestion of five mercupurin tablets until April 5, 1945, when the program of one tablet three times a day for five days a week was reinstituted because the patient believed that the urine volume was greater with the latter method of administration. He did well until April 19, 1945, when his supply of tablets was exhausted and for one week he was without them. Signs and symptoms of congestive heart failure recurred and required two intravenous injections of mercupurin at weekly intervals while he resumed the ingestion of the tablets three times a day for five days a week. Since then he has been free of congestive heart failure on this regimen. He has shown no evidence of mercurialism. Urine examinations have been repeatedly negative.

This case illustrates persistent congestive heart failure after myocardial infarction, despite repeated intravenous injections of mercupurin. No congestive failure occurred while taking mercupurin tablets. After the supply of tablets was exhausted and with development of a respiratory infection, recurrence of congestive heart failure was relieved by resumption of the mercupurin tablets and by several doses of mercupurin administered intravenously; the continuance of tablets orally was effective.

Case v. W. D., a sixty-four-year old man with severe congestive heart failure and diabetes mellitus, was hospitalized from January 18, 1946 to February 10, 1946, with improvement on a regimen of bed rest, digitalization and insulin. The symptoms and signs of congestive heart failure soon recurred and persisted in spite of weekly injections of mercupurin. On May 16, 1946, he was started on three mercupurin tablets every morning before breakfast with striking improvement. Since then he has been free of congestive heart failure. He has shown no evidence of mercurialism. Albumin has been present consistently in slight amounts and the sediments were negative.

This was a patient with persistent congestive heart failure despite repeated injections of mercupurin; he showed dramatic response to therapy with oral mercupurin tablets.

Case vi. J. G., a fifty-six-year old man with luetic heart disease, congestive heart failure and angina pectoris, did not improve on the usual treatment for congestive heart failure. On December 14, 1944, he was given one mercupurin tablet three times a day in addition to his other treatment, with marked improvement of congestive failure. On January 5, 1945, he developed bloody stools and cramps and the mercupurin tablets were omitted for several days. At this time the dyspnea on effort was markedly improved. In February and March, 1945, he had bouts of diarrhea and cramps, each lasting one day but the mercupurin tablets were continued. Following an upper respiratory infection in March, 1945, the nocturnal anginal attacks with dyspnea increased. Beginning in April, 1945, he was free of dyspnea but continued to suffer with angina by day and at night. In August, 1945, on three occasions he had diarrhea lasting one day. On October 4, 1945, he died suddenly. Throughout the period of observation the urine showed slight amounts of albumin and the sediments were negative.

This case illustrates persistent congestive failure in spite of mercupurin injections in a patient with luetic heart disease. Mercupurin tablets relieved the congestive heart failure but the anginal attacks persisted and the patient died suddenly.

CASE VII. M. O., a seventy-four year old man with aortic stenosis and insufficiency, as well as angina pectoris, was hospitalized in June, 1943, for progressive congestive heart failure of six months' duration. With rest in bed, low salt diet, digitalization, ammonium chloride, four intravenous injections of 2 cc. mercupurin and bilateral thoracentesis he rapidly improved. In September, 1943, and January, 1944, he was readmitted because of recurrent congestive heart failure and on a similar therapeutic program, including six intravenous injections of 2 cc. mercupurin, he improved but continued to have frequent angina pectoris. In October, 1944, congestive heart failure recurred, for which he was given intramuscular injections of 2 cc. mercupurin on October 5, 1944, November 16, 1944 and November 30, 1944, with good diuretic responses. Following the last injection one mercupurin tablet twice a day was given with good effect. On December 7, 1944, the dose was increased to three tablets every morning. On December 14, 1944, he reported a brief period of abdominal cramps with one bowel movement a day. On December 21, 1944, he complained of pain and an itchy feeling in the gums with anorexia. No symptoms or signs of congestive heart failure were observed. The mercupurin tablets were omitted until January 11, 1945, when the gums were normal but the patient complained of dyspnea. An intramuscular injection of 2 cc. mercupurin was given at this time and one mercupurin tablet three times a day for five days a week was resumed. On this regimen he did well until May 1, 1945, when he again complained of pain in the gums and teeth. The lower gums were spongy and covered with exudate; there was no mercury line. The mercupurin tablets were omitted from May 17, 1945 to June 28, 1945, during which time the gums became normal except for pyorrhea. However, congestive failure recurred and two mercupurin tablets every other morning were resumed; the congestive failure cleared up. On August 30, 1945, the dosage of mercupurin tablets was reduced to one tablet every other morning to determine if the patient would remain symptom-free on the smaller dosage. Because he developed dyspnea on effort, on September 20, 1945 the dosage of mercupurin tablets was increased to two every other morning. On October 4, 1945, after his supply of mercupurin tablets was exhausted for three days he again developed recurrence of dyspnea on effort and also paroxysms at night which woke him from sleep. Mercupurin tablets, one daily, were resumed and he did well until January 14, 1946, when exertional and paroxysmal nocturnal dyspnea recurred. Intramuscular injections of 2 cc. mercupurin were given on January 31, 1946, February 7, 1946 and February 14, 1946, with good diuretic responses and the patient became free from symptoms. On March 14, 1946, the dosage of mercupurin was increased to two tablets five times a week and the patient became free from symptoms of congestive heart failure. On July 5, 1946, the patient expired in his sleep. Minimal albuminuria was present throughout the period of observation.

This patient had recurrent congestive heart failure with aortic stenosis and insufficiency and angina pectoris. Mercupurin tablets relieved the congestive heart failure but did not alter the angina pectoris; the patient died suddenly.

CASE VIII. M. P., a sixty-five year old man with hypertension and angina pectoris since 1935, developed congestive heart failure in 1941. He was hospitalized from May 13, 1942 to June 2, 1942, for the treatment of congestive heart failure. With rest in bed, a salt-poor diet, digitalization and thesodate tablets he rapidly improved. Mercurials were not necessary. Five months following his discharge the symptoms and signs of congestive heart failure recurred in spite of continuance of treatment and beginning in January, 1943, intravenous mercurials were given at weekly or bi-weekly intervals. In November, 1944, in spite of this treatment and occasional urea administration, the signs and symptoms of congestive heart failure required two intravenous injections of mercurials a week. At the same time he was given one mercupurin tablet twice a day. After one week severe orthopnea recurred and the dosage of mercupurin tablets was increased to three every morning before breakfast. After one week the mercupurin tablets were discontinued because they pro-

duced no demonstrable effect. The mercurial injections were continued semiweekly until February, 1945, when he took five mercupurin tablets twice weekly for two weeks without any effect. The mercurial injections were then given weekly or semiweekly throughout the remainder of 1945 and up to October 10, 1946. For one week in May, 1946, he was given three mercupurin tablets each morning without any demonstrable effect. Beginning on August 1, 1946, after he had been receiving semiweekly injections of mercurials for a month, he was given two mercupurin tablets every morning before breakfast. Beginning August 8, 1946, the dose was increased to three tablets every morning. Improvement of the congestive heart failure resulted but he still required weekly injections of mercurials. Because of recurrence of severe congestive heart failure he was hospitalized in October, 1946, with marked improvement. Since his discharge he has taken digitalis, ammonium chloride and three mercupurin tablets each morning and has been free from congestive heart failure. Urine examinations revealed moderate albuminuria and negative sediments throughout his illness.

This was a patient with chronic congestive heart failure who required weekly or semiweekly injections of mercurials. Because the results were not satisfactory, oral mercupurin was given but with poor results because of gross congestive heart failure. After adequate treatment of congestive failure in the hospital, oral mercupurin was effective.

CASE IX. G. P., an extremely obese forty-four year old man, had an attack of posterior myocardial infarction in 1934. In 1941 and 1943, he was admitted to another hospital because of congestive heart failure, obesity, alcohol addiction and hypertension. Treatment consisted of digitalization, rest in bed and intravenous injections of mercurials. He was admitted to the Beth Israel Hospital in February, 1944, because of increasing congestive heart failure of two to three weeks' duration as well as angina pectoris. With rest in bed, digitalization, four intravenous injections of mercupurin, ammonium chloride and an 800 calory low-salt diet, the patient improved dramatically. He was again hospitalized in August, 1944, for treatment of severe congestive heart failure, with marked improvement. After his discharge from the hospital he was treated with digitalis, ammonium chloride, a low-salt diet, vitamin B complex and thiamin chloride. Two cc. of mercupurin were given intramuscularly and repeated on November 2 and November 9, 1944, for signs of congestion. On March 30, 1945, he was again in severe congestive heart failure, having omitted all medication, and he was again hospitalized, with improvement. Congestive failure recurred and hospitalization was again necessary in October, 1945. He was started on three mercupurin tablets every other morning before breakfast, in addition to the other treatment. On this regimen he was free from signs and symptoms of congestive heart failure until May 2, 1946, when he reported that his supply of mercupurin tablets had been exhausted one week previously. At this time he felt very well and showed slight edema of the legs. He was given 2 cc. mercupurin intramuscularly and was instructed to resume the former plan of therapy. On May 16, 1946, he felt well but because of the presence of a slight amount of fluid at both lung bases and slight edema of the legs, he was given 2 cc. mercupurin intramuscularly. The dosage of mercupurin tablets was increased to three every morning before breakfast. On May 23, 1946, he still showed evidence of fluid in both lungs and slight edema of the legs. Two cc. of mercupurin were administered intramuscularly. On June 26, 1946, he felt well but he showed slight edema of the legs and 2 cc. of mercupurin were administered intramuscularly. On August 15, 1946, he presented less edema of the legs and received 2 cc. mercupurin intramuscularly. On September 19, 1946, he was free from signs and symptoms of congestive heart failure. On December 16, 1946, he suffered with an attack of nocturnal paroxysmal dyspnea after a very heated argument. Since then he has been free of congestive heart failure. Repeated urine examinations during the period of oral mercupurin therapy revealed no albumin.

This was a patient with recurrent severe congestive heart failure and coronary and hypertensive heart disease who required frequent hospitalization. The patient obtained complete freedom from signs and symptoms of failure on oral mercupurin therapy. After the supply of tablets was exhausted there was a recurrence of signs of congestive heart failure which were relieved by resumption of the mercupurin tablets and several doses of mercupurin administered intramuscularly; the continuance of tablets was effective.

CASE X. J. S., a seventy-one year old man with hypertensive heart disease, developed congestive heart failure in April, 1944. He was digitalized but was not very cooperative. In April, 1945, he had severe congestive heart failure. He was redigitalized and ammonium chloride and a low salt regimen were prescribed. An intravenous injection of 2 cc. mercupurin was given on April 26, 1945 and May 3, 1945, with profuse diuresis with recurrence of symptoms and signs of congestive heart failure between injections. On May 10, 1945, he received an intravenous injection of 2 cc. mercupurin and mercupurin tablets were started with a dosage of one tablet three times a day for five days a week. Congestive heart failure recurred and on May 17, 1945, an intravenous injection of 2 cc. mercupurin was given and three mercupurin tablets every other morning were prescribed. Because the congestive heart failure could not be controlled with weekly intravenous injections of mercupurin, mercupurin tablets, digitalis and ammonium chloride the patient was admitted to the hospital on June 25, 1945. With rest in bed, digitalis, low-salt regimen, ammonium chloride and three intramuscular injections of mercupurin he rapidly improved and was discharged on July 11, 1945. On July 19, 1945 and July 26, 1945, he received an intravenous injection of 2 cc. mercupurin and he took three mercupurin tablets three days after each injection. On August 2, 1945, he received an intravenous injection of 2 cc. mercupurin and the mercupurin tablets were resumed, three every other morning before breakfast. In October, 1945, after a prolonged attack of nocturnal paroxysmal dyspnea, the digitalis was increased to 0.2 Gm. daily. Thereafter, he was free of signs and symptoms of congestive heart failure until April, 1946, when after omitting the mercupurin tablets for one week he developed sudden onset of dyspnea and was admitted to another hospital. Examination there revealed evidence of mild congestive heart failure. After his discharge he was observed there until October 10, 1946, when he returned to us for a follow-up visit. He reported that in the six months' interval he received intramuscular injections of mercupurin, digitalis 0.1 Gm. daily, ammonium chloride but no mercupurin tablets; he had dyspnea on effort and no edema.

This was a patient with hypertensive heart disease and congestive heart failure who improved rapidly on a regimen of weekly intravenous injections. Mercupurin tablets were started during gross congestive failure but were ineffective. He was hospitalized with resultant clearing of the congestive failure; he was then maintained on mercupurin tablets and was in a greatly improved condition. Recurrence of congestive failure occurred when the tablets were discontinued.

CASE XI. I. W., a sixty-eight year old woman with congestive failure, nodular thyroid, blood pressure of 224/125, great enlargement of the heart and basal metabolic rate of +10 per cent, had a total bilateral thyroidectomy on November 6, 1944. Two weeks after her discharge she developed exertional dyspnea and orthopnea as well as edema of the legs. She was readmitted to the hospital on December 26, 1944, for treatment of congestive heart failure, with improvement. Intravenous injections of 2 cc. mercupurin were continued after discharge and in April and May, 1945, there was no evidence of congestive failure. On January 3, 1946, moderately severe congestive heart failure was again evident. On January 24, January 31, 1946 and February 7, 1946, intramuscular injections of 2 cc. mercupurin were given but the congestive heart failure became more severe and she was hos-

pitalized from February 11, 1946 to March 5, 1946. On March 21, 1946, she developed moderately severe congestive heart failure after a respiratory infection. An intramuscular injection of 2 cc. mercupurin was given and mercupurin tablets, three every other morning before breakfast, were prescribed. Because of slight edema of her legs a parenteral dose of mercupurin was given on April 25, 1946. She improved remarkably and has continued to be free from signs and symptoms of congestive heart failure. From August, 1946 to December, 1946, she was aware of a lack of appetite and slight nausea without cramps or diarrhea on the days she took the mercupurin tablets. Since December, 1946, she has taken the three mercupurin tablets every other evening at bedtime and has been free of nausea and anorexia, as well as of congestive heart failure. The urine examinations have shown slight to moderate amounts of albumin with negative sediments.

The patient had recurrent severe congestive heart failure with marked hypertension and great cardiac enlargement which required frequent hospitalization. She has had complete freedom from symptoms and signs of failure since institution of oral mercupurin therapy; parenteral mercurials were not necessary during this period.

SUMMARY

1. The oral administration of mercupurin tablets is valuable in the treatment of ambulatory patients with chronic congestive heart failure.

2. Oral administration of mercurial diuretics may be more practical and more effective than parenteral administration in some ambulatory patients with chronic or recurrent congestive heart failure.

3. The method of administration and dosage must be individualized to obtain satisfactory results.

4. Minor toxic manifestations occur in some patients but offer no serious obstacle to the continuance of treatment, provided that the patients are carefully followed.

5. One instance of severe mercurialism was observed which makes it necessary to stress the importance of adequate supervision of patients receiving this drug. Unless patients can be seen once a week for the necessary clinical and laboratory examinations, oral mercupurin therapy should not be used.

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Review

Pathogenesis of Peripheral Cardiac Edema*

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OVER a period of many years the pathogenesis of cardiac edema has interested physiologists and clinicians. The more recent studies of peripheral edema have not only elaborated upon and expanded older conceptions but these investigations also have suggested other possible mechanisms of edema formation. The subject is of sufficient current interest and the significant contributions are so widely scattered in the literature that a general survey of the question now seems warranted.

A century ago, James Hope[34] attempted to explain the symptoms and signs of cardiac decompensation on the basis of pulmonary and systemic venous stasis from failure of the weakened heart. Studies with the heart-lung preparation suggested to Starling[73] that cardiac failure leads directly to an increase in venous pressure. In the ensuing years, the importance of venous engorgement was emphasized by a number of observers, including many French and German clinicians (Harrison[30]).

In recent years, the hypothesis that venous engorgement is primarily concerned in cardiac edema has been championed by Harrison[30] under the designation of "backward failure." Harrison maintained that elevated venous pressure is the result of the impounding blood in the systemic veins as the ability of the heart to pump blood forward becomes impaired. The rise in venous tension then leads to increased capillary pressure, augmented filtration and thence edema. Increased capillary permeability, partial lymphatic obstruction and decrease in plasma proteins have been suggested as secondary factors in such tissue fluid retention.[19,30]

Although it has been widely held that congestive phenomena dominate the mechanisms producing the edema of heart failure, there is a growing body of evidence to indicate that certain signs of cardiac failure arise in consequence of altered cardiac output. Nearly one hundred years ago, Stokes[77] emphasized the importance of myocardial weakness as the precipitating factor in heart failure. Mackenzie,[50] in later years, suggested that the primary cause of the symptoms of cardiac insufficiency is a deficient blood supply to the tissues. In the light of newer researches into the mechanisms of cardiac failure, these older suggestions have assumed new significance. In contrast to the older hypothesis of "backward failure," the conception of "forward failure" of the heart, as it may be conveniently designated, has been regarded with increasing interest in recent years.

The forward failure hypothesis has been elaborated upon by the work of Warren, Stead and associates.[81] These investigators called attention to the well known fact that subclinical or occult edema is present earlier in heart disease than is frank edema. They suggested that elevation of venous tension may occur later than extracellular fluid retention; therefore, increased venous pressure may be of secondary importance in the pathogenesis of edema. In addition, they suggested that renal function may be disturbed during cardiac failure so that sodium chloride is retained by the kidneys. Reten-

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tion of fluid by the body tissues then ensues. (Fig. 1.)

The clinical and experimental evidence of the various suggested mechanisms of edema formation will be briefly reviewed.

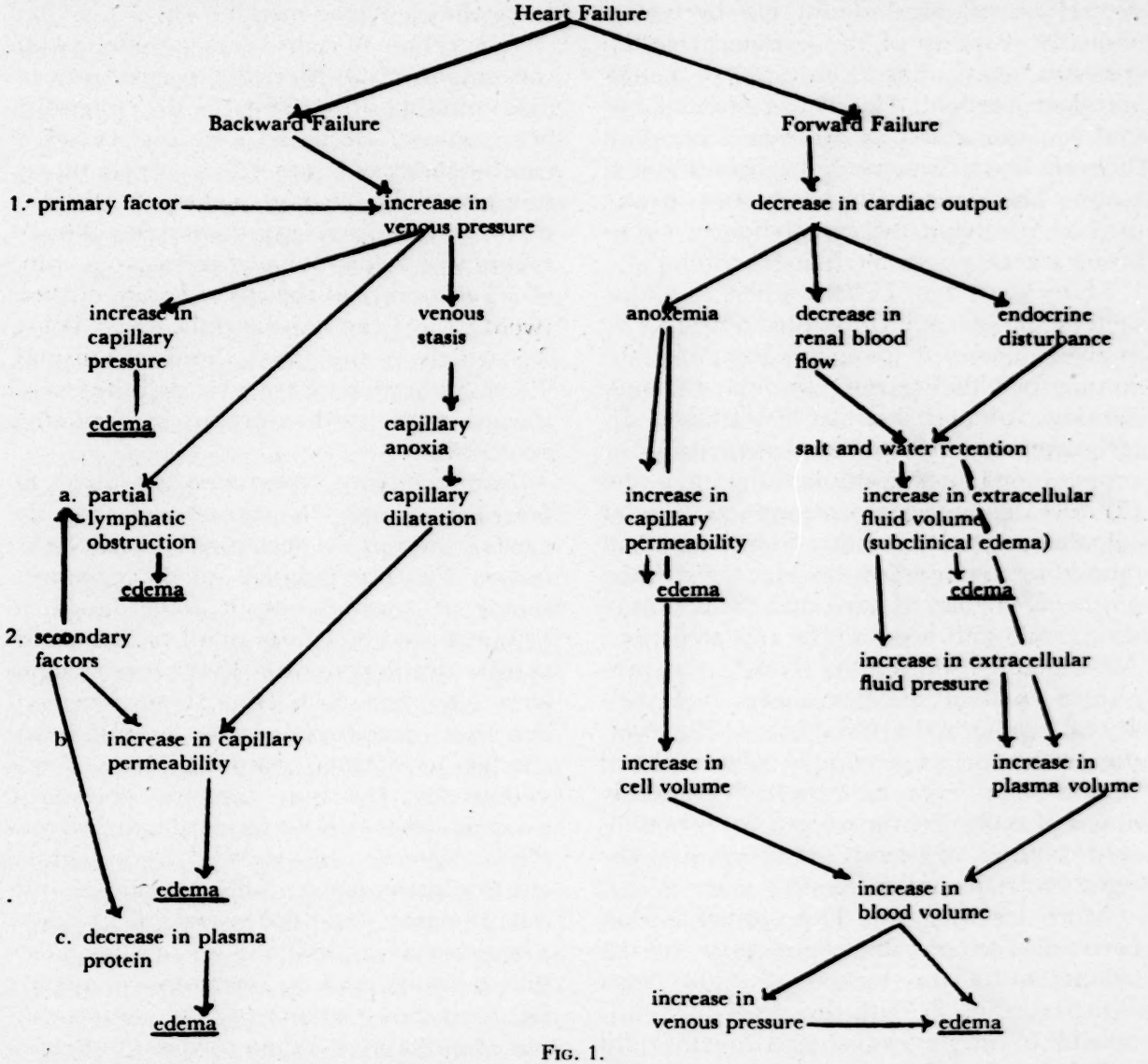

FIG. 1.

Cardiac Output. The output of blood by the heart during cardiac decompensation is suggested as of primary importance in a consideration of the mechanism of edema formation. The very basis for a theory of "forward failure" must obviously depend upon the demonstration of diminished cardiac output. Investigators have endeavored for years to evolve an accurate method for the determination of cardiac output in man. Such efforts have been fraught with difficulty and have not yielded uniform results. In 1929, Grollman[28] evolved the acetylene technic which was subsequently utilized by a number of workers as the most accurate procedure. Harrison,[30] in a summary of the evidence obtained by this method, enumerated four important considerations: (1) apparently normal subjects may have a low cardiac output; (2) the cardiac output may be elevated, diminished or normal in patients with congestive heart failure; (3) average values and ranges of cardiac output are similar in cardiac patients with and without heart failure and (4) with clinical

improvement and disappearance of edema there may be an increase, decrease or no change in the output of the heart. These findings suggest that the cardiac output is not consistently decreased during heart failure. However, some doubt has been cast upon the validity of this evidence by the criticism which has been leveled at the acetylene method. Hoff[32] has pointed out that a major source of error may occur in the technic, in the matter of recirculation of blood. The same criticism applies to any method involving the calculation of circulating substances in the blood stream.

Many years ago, Fick[18] evolved a unique method of determining cardiac output. The method depended upon calculation of the volume of blood passing through the pulmonary vascular bed as determined by measuring (1) the uptake of oxygen by the venous blood passing through the lungs and (2) the rate of oxygen consumption. Similar calculations may be made from equivalent data concerning carbon dioxide. The method has been extensively used and the details of the calculations need not be repeated here. As originally utilized by Fick,[18] the procedure entailed the gas analyses of peripheral venous and arterial blood. However, the utilization of a sample of peripheral venous blood from one extremity obviously may not represent the oxygen or carbon dioxide content of venous blood entering the right ventricle and pulmonary artery.[19]

More recently the Fick principle has become of inestimable value with the development of the technic of right heart catheterization.[20] With this procedure, it is possible to sample venous blood from the right auricle or ventricle. Arterial blood is obtained from a convenient point in the periphery. The cardiac output can be determined with greater accuracy than by use of the acetylene technic. Klein[38] was one of the first workers to measure cardiac output in man by this method but it was not used extensively until recently because of the danger to the patient which was thought to accompany the procedure. Cournand and his associates,[9] using the same method, reported studies of cardiac output in thirteen normal subjects. They obtained average values for the cardiac index* of 3.12 L. per sq. m. per min. These values were 26.8 per cent higher than those previously reported using the acetylene method.

The technic of right heart catheterization was employed by Merrill[54] to measure cardiac output in patients with congestive heart failure. He found a normal range of cardiac index of 2.3 to 4.1 (L. per sq. m. per min.) with an average value of 3.3. The cardiac index in twenty-three cases of heart failure was below the average normal value of 3.3 in twenty of the cases. In ten of these twenty cases the cardiac index was below 2.3 which is the lower limit of normal. These data demonstrate a definite trend toward a low cardiac output in congestive heart failure.

Two criticisms have been advanced by Harrison against the contention that the cardiac output is decreased during heart failure. First, he pointed out that measurements of cardiac output have failed to demonstrate low values in all patients with cardiac decompensation. Furthermore, cases were cited in which clinical improvement was not accompanied by a significant change in cardiac output. These observations by Harrison are not necessarily irreconcilable with the forward failure hypothesis. Several workers[19,29,54] have pointed out that many factors influence cardiac output; all cases would not be expected to show a decrease at any given moment during cardiac decompensation. For instance, anxiety has been shown to increase the cardiac output remarkably.[76] When cardiac compensation was accomplished with mercurial diuretics in the cases cited by Harrison, the output might not be expected to change.[54] Merrill[54] used digitalis to abolish heart failure. All of six patients then showed an increase in cardiac output.

Second, Harrison called attention to patients with peripheral circulatory collapse in whom the cardiac output was markedly de-

* Cardiac index is the minute volume output of the heart per square meter of body surface.

creased and the clinical picture was not that of heart failure, with dyspnea and edema. Merrill[54] answered the second objection in indicating that the duration of shock is usually too short to permit the accumulation of salt and water to occur. Edema develops if shock is prolonged.[54,55]

Renal Blood Flow. It has been known since the time of Richard Bright that certain forms of renal disease are accompanied by peripheral edema. For many years clinicians believed that edema from kidney disease and heart failure was produced by quite different mechanisms. However, the experimental and clinical evidence of recent years has suggested that the part played by the kidney in the pathogenesis of cardiac edema may be of some significance. The possibility of such a "renal factor" is indicated in the observations of Fremont-Smith.[21,22] He noted that ingestion of large amounts of water by patients with cardiac edema resulted in greater dilution of the blood and less diuresis than occurs in normal persons.

An interesting conception of the rôle of the kidneys in the pathogenesis of cardiac edema was offered by Warren and Stead[81] in 1944. They suggested that under the impact of decreased cardiac output, diminished renal flow impairs the excretion of salt by the kidneys and that such sodium chloride retention provokes abnormal water storage and the formation of edema. The evidence supporting this conception will be presented in some detail.

In recent years, improved methods of measuring renal blood flow have been developed. A preliminary report by Warren and Stead[82] demonstrated that a reduction in blood flow through the kidney occurs in the course of heart failure. To determine renal blood flow, (1) they used the para-amino hippurate clearance technic, and (2) they catheterized the renal vein in man in order to obtain renal venous blood for measurement of its oxygen content. An increase in the arteriovenous oxygen difference in the kidney during congestive heart failure was interpreted as indicating that the quantity of blood passing through the kidney was reduced. Merrill[54] also employed the para-amino hippurate clearance method to study renal blood flow in a series of patients with cardiac decompensation; he found a marked reduction in renal flow in each case. Glomerular filtration rate decreased less than the renal blood flow; this resulted in a high filtration fraction which suggested to Merrill that efferent arteriolar constriction had occurred. Since renin is known to cause efferent arteriolar constriction,[56] Merrill[55] bio-assayed the blood for renin in patients with heart failure. He found a significant amount of renin in renal venous blood in eight of eleven patients.

Merrill's study indicated that the reduction in renal blood flow was usually proportionately greater than the decrease in cardiac output. He ascribed this reduction to the diversion of blood from the kidney. The increase in renal blood flow accompanying clinical improvement in some of these patients was not marked because compensation was accomplished by means of mercurial diuretics alone and the cardiac output remained low. Phenol red clearance studies by Seymour and his co-workers[69] showed an increase in renal blood flow of approximately the same degree as the cardiac output when compensation was accomplished with digitalis.

Unfortunately, it is difficult to prove a direct correlation between reduced renal blood flow and the pathogenesis of cardiac edema for it may be argued that the changes in the renal circulation are secondary to an increase in venous pressure. Nevertheless, Merrill's results support the pathogenic rôle played by diminished renal flow in that: (1) no significant correlation between the level of venous pressure and renal flow occurred and (2) the renal blood flow remained below 50 per cent of normal in most cases, despite a marked reduction in venous pressure.

The question now arises as to whether reduced renal blood flow will lead to salt retention. Reaser and Burch,[61] using radioactive sodium, demonstrated a marked impairment in sodium excretion in patients with cardiac decompensation. Futcher and

Schroeder[23] found that patients in congestive heart failure excrete only 30 per cent as much salt as normal subjects when large amounts of salt are given by venoclysis. These observations suggested a disturbance in salt metabolism during cardiac insufficiency. Futcher and Schroeder tentatively suggested that a circulatory disturbance in the kidney may lead to renal anoxemia and that an increase in the rate of tubular reabsorption of sodium chloride occurs. However, actual determinations of tubular reabsorption show that it is normal or slightly decreased during heart failure.[54] The studies of Seymour and his co-workers[69] also showed that tubular function does not appear to be greatly impaired during heart failure. They found no change in the concentrating power of the kidney during cardiac compensation.

Possibly a more satisfactory explanation of salt retention is a low glomerular filtration rate secondary to definite reduction in renal blood flow. Merrill[54] demonstrated that glomerular filtration (inulin clearance) may be reduced 33 to 50 per cent of normal in patients with cardiac insufficiency. This study may indicate that the quantity of sodium filtered by the glomerulus is decreased. Then if tubular resorption is essentially normal during heart failure and reduced sodium filtration occurs, sodium ions must be retained in the body. The sodium retention affects body water retention and a corresponding increase in blood and tissue fluid volume results. Therefore, it is easily understood that with the patient in heart failure who continues to use an average salt-containing diet, retention of sodium chloride and water may be enhanced and clinical edema of varying degree may ensue. In addition, it has been pointed out[54] that glomerular filtration rate may be very low in chronic nephritis and, in such cases, edema may be marked although not invariably so.

Venous Pressure. According to the hypothesis of "backward failure," venous engorgement results from the impounding of blood in the systemic veins. The events which may lead to an elevated venous pressure are summarized in considering the development of congestive heart failure in a patient with hypertension (Harrison[30]). Let us assume that the left ventricle normally expels 40 cc. of blood per beat. As a result of hypertension, the myocardium weakens and the left ventricle expels only 39 cc. Inflow continues to be 40 cc. so that the left ventricle receives more blood than is expelled. Dilatation of the left ventricle then occurs and the ventricular pressure rises. A difference in the pressure between the left ventricle and auricle occurs so that the blood received by the left ventricle is reduced to 39 cc. per beat. Since the left auricle is highly distensible, it dilates to retain blood before the pressure eventually rises. Fibers of the left ventricle, under the stretch of dilatation, contract more strongly and are again able to deliver 40 cc. of blood per beat. Equilibrium is temporarily restored with the same cardiac output, a larger diastolic heart size and a higher pulmonary venous pressure. Extension of this process to include the right ventricle and the right auricle results finally in an increase in the pressure in the systemic veins.

Harrison contended that this explanation of the symptoms of heart failure is the most satisfactory.[30] To illustrate, he reasoned that congestive phenomena should occur first in the lungs and later in the systemic circulation. In support of this hypothesis is the added finding that a decrease in vital capacity may precede an elevation of venous pressure.[30]

Recent studies by Landis and his associates[45] have emphasized again the mechanical elements concerned in the elevation of venous pressure in heart failure. In their clever experiments, they "exercised" normal anesthetized dogs by applying appropriate electrical stimuli to the extremities, producing muscular motion. During such muscular activity a fall in venous pressure occurred. However, when the hearts of dogs were previously damaged by interference with the coronary circulation, such muscular activity produced a rise of venous pres-

sure. This evidence suggested to them that chronic congestive heart failure might result from repeated episodes of increased muscular activity in individuals with impaired cardiac "competence." During these periods blood accumulates in the systemic veins due to back pressure, leading to increased transudation into the tissues. Thereafter, a reduction in "effective blood volume" occurs due to impounding of blood in the venous system with compensatory systemic vasoconstriction and retention of salt by the kidneys. Landis et al., reasoned that "the division between 'backward failure' and 'forward failure' becomes somewhat less rigid because the former may, through changes in effective blood volume, lead during activity to the latter."

Many workers[1,54,55,70,74,75,81] have considered backward failure and venous engorgement an unduly simple explanation and have suggested that additional factors are probably concerned. Ryder[65] reported that an elevated tissue pressure may exert considerable influence on venous tension. Evidence indicates that tissue pressure is elevated in cardiac failure and some observers[74,75] have suggested that venous hypertension may be partially referable to such elevated tissue tension. It has also been demonstrated that an increase in intrapleural pressure (occurring as in hyperpnea or Valsalva effect) contributes to the elevation of venous tension.[9,23,84] These factors do not appear to be essential to the increase of venous pressure accompanying cardiac failure but they may be of some significance.

Of some interest is the possibility that changes in venous pressure occur because of redistribution of blood within the vascular bed from alterations in the tone of the vascular system.[4,55] Certain clinical observations, such as the maintenance of a normal blood pressure in the presence of decreased cardiac output and the early fall in venous pressure which occurs in response to digitalis, indicate that vasoconstriction occurs.[55] Additional evidence for active vasoconstriction is the increased peripheral resistance frequently noted during cardiac decompensation.[69]

The pathogenesis of vasoconstriction in congestive heart failure is not satisfactorily understood. Forward failure theorists have suggested that vasoconstriction may be secondary to decreased cardiac output.[55] On the other hand, Landis maintained that the vasoconstriction is compensatory in reaction to venous engorgement. Renin, which has been found in renal venous blood of patients with heart failure,[55] may be related to the vasoconstriction but this relation is not clear.

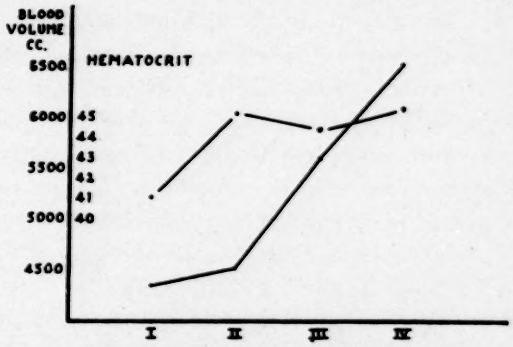

FIG. 2. Changes occurring in blood volume and hematocrit as the degree of cardiac decompensation increases (Gibson and Evans, 1937).[24] Group I consisted of patients with valvular heart disease who exhibited no symptoms or signs of cardiac insufficiency. Group II included those with mild symptoms of cardiac decompensation. In groups III and IV the patients were in severe congestive heart failure. ——— and —·— are symbols for blood volume and hematocrit, respectively.

Another factor which has been considered of importance in explaining the mechanism of venous hypertension is increased blood volume. That hypervolemia occurs during congestive heart failure is well established. Gibson and Evans,[24] using a dye method, studied seventy-three patients with clinically proved heart disease. (Fig. 2.) A marked elevation of blood volume occurred as the degree of heart failure increased although the hematocrit remained almost unchanged. These findings indicated that cell volume increased in nearly the same order of magnitude as the plasma volume. The experiments were confirmed by the observations of Walker et al.[80] and by Meneely and Kaltreider.[53] The latter authors noted a high correlation between the degree of anoxemia and the increase in cell volume.

Observations by Landis and his co-workers[45] do not support the hypothesis that hypervolemia is the principal factor leading to venous hypertension. They increased the blood volume in normal dogs from 50 to 100 per cent by transfusion and found only a transient elevation in venous tension. In these transfused dogs, a sustained rise in venous pressure did not occur during exercise. On the other hand, Starr and his associates[74,75] found that the venous pressure of patients with heart failure remained elevated after death; therefore, they reasoned that postmortem persistence of venous hypertension must be due to increased volume of fluid in the vascular bed.

The time relationship of the appearance of an elevation of venous pressure to the rise in plasma volume and the onset of edema is of considerable importance. If the plasma volume increases and subclinical or frank edema occurs *before* the venous pressure becomes elevated, then hypervolemia may be the principal cause of elevated venous pressure. In order to investigate this question, Warren and Stead[81] studied two cardiac patients as they developed "heart failure" following salt administration. The data of one case are presented:

The case was that of a fifty year old negro man with hypertensive and arteriosclerotic heart disease in severe heart failure. With treatment, including digitalis, bed rest, diuretics and a salt-free diet cardiac compensation was restored. Thereafter, salt was added to his diet; diuretics were omitted but he continued to receive digitalis. During the following nine days an increase in plasma volume and in body weight occurred but the venous pressure remained essentially unchanged.

In these two cases, the curves of weight and plasma volume were essentially parallel, indicating that elevation of venous pressure does not necessarily accompany hypervolemia and the formation of edema.

Several investigators have demonstrated that errors occur in the use of the T-1824 dye technic for plasma volume determination.[17,25,27] This method was used in the above described observations. The loss of dye into the extracellular spaces or lymphatic system during mixing and the infiltration of dye into the renal and hepatic parenchyma are objections to this method.[17,25,27,46] Hopper and his co-workers[35,36] concluded that this method was valuable only for demonstrating gross changes in blood volume and not for determining absolute values. Since Warren and Stead studied only two cases and since the dye method is not considered completely reliable, one is rather hesitant to accept their evidence of the temporal relation of venous pressure and plasma volume changes as conclusive. Their observations, however, are suggestive.

Another question arises concerning the evaluation of the evidence of Warren and Stead. Certain factors of heart failure (e.g., rise in venous pressure and a gain in weight) appeared in patients with compensated heart disease following salt administration. Lyons et al.[49] and Grant and Reichsman[26] showed that administering salt to normal subjects will result in an increase in venous pressure, plasma volume and weight. If indeed this occurs in normal individuals, one wonders whether the changes that occurred in the two cases of Warren and Stead represent true congestive heart failure. The problem cannot be answered definitely but it is true that the clinical picture in these cases closely simulated heart failure.

That salt and water retention occurs in heart failure is supported by the observation that an increase in weight and the appearance of edema may occur prior to the elevation of venous pressure. An increase in weight preceded the rise of venous pressure in the two cases of Warren and Stead[81] and Altschule[1] found that seven of fifteen patients with edema had venous pressures of 75 mm. of saline or less. There are other reports in which elevation of venous pressure and edema were not associated[2,3,37,63] or did not correspond in magnitude. In some cases, the disappearance of edema was followed, and not preceded, by a lowering of venous pressure. Such findings point to the possi-

bility that an increase in venous pressure may not be the primary factor in the formation of edema.

Clinical observations offer additional evidence that retention of extracellular fluid precedes a rise in venous pressure. Patients with paroxysmal nocturnal dyspnea, without venous engorgement and clinical edema, may show striking improvement when the urinary output is increased by the use of mercurial diuretics.[19] In left-sided heart failure, dyspnea and orthopnea may develop before the venous pressure becomes elevated yet there is often subclinical edema as shown by weight gain. A decrease in weight of several kilograms may occur with restoration of cardiac compensation.[81]

In contrast, Reichsman and Grant[62] studied the temporal relation of the appearance of elevated venous pressure, increase in weight and edema in three patients with "inactive" rheumatic heart disease. These patients were in congestive heart failure upon entrance to the hospital; cardiac compensation was accomplished with digitalis and a low salt diet. Digitalis medication was then discontinued. They found that a rise in venous pressure preceded the gain in weight and the appearance of edema in each of these patients. The omission of digitalis from the therapeutic regimen allowed the myocardium to fail again. Consequently, this experiment more closely simulates naturally occurring heart failure than the one performed by Warren and Stead. The observations of Reichsman and Grant support the back pressure hypothesis. Another interpretation of thesefindings is that the rise in venous pressure may be the result of redistribution of blood in the venous system produced by venoconstriction.[54]

The question of the temporal relation of venous hypertension to edema formation has not been conclusively answered. Further experiments with particular reference to venous pressure determinations are desirable. It would be preferable to measure right auricular pressure instead of venous pressure but the technical difficulty of this procedure makes it impractical for repeated use in the same patient. To establish conclusively the time relation of elevated venous pressure and edema, a large series of cases must be studied.

Whatever the origin of venous engorgement, it seems that an elevation of venous pressure to a certain critical level will produce peripheral edema.[12,40,52] Mende[52] noted that if the escape of blood from an extremity was prevented, edema could be demonstrated when the volume of the leg was increased by 10 per cent. Drury and Jones[12] confirmed Mende's observation. Krogh, Landis and Turner[40] reported that fluid accumulates in the extracellular tissue spaces of man as the venous pressure becomes greater than 15 to 20 cm. of water.

Capillary Pressure. When the venous tension rises sufficiently during failure of the heart, one may visualize the pressure as distending the venules and capillaries with transudation of fluid into the tissues. That such a mechanism may indeed operate to foster edema was suggested by the experiments of Starling fifty years ago.[72,73] His concept taught that two factors—the hydrostatic venular and capillary pressure and the colloid osmotic tension of the plasma oppose each other constantly. By this mechanism fluid is held in abeyance between the fine blood vessels and the extracellular tissue spaces. Should the hydrostatic pressure exceed that of colloid osmotic force, transudation of fluid into the tissues occurs. Conversely, elevation of colloid osmotic pressure permits fluid to leave the tissue spaces and enter the circulation. Such a concept has dominated the thinking of clinicians for many years.

Some of the studies, using crude methods, failed to show any correlation between venous and capillary pressure.[5] Landis,[43] however, studied the capillary pressure in normal subjects by a micromethod of cannulating capillaries. The inflation of pneumatic cuffs applied to the extremity produced a rise of capillary pressure corresponding to the rise in venous pressure. Fahr and Ershler,[15,16] employing Landis' technic, studied the pressure in the capillaries of the skin in

patients with predominant right ventricular failure. (Table 1.) The mean colloid osmotic pressure in this group of patients was 21 to 22 mm. Hg. In their studies, the venous capillary pressure was higher than the colloid osmotic pressure in all but one instance (Case 8). Since it is known that under normal conditions filtration occurs only from the arterial limb of a capillary loop,[43] the elevated venous capillary tension in these observations indicated that filtration occurred along the entire capillary loop. Fahr and Ershler concluded that the factor of increased capillary pressure satisfactorily explained the formation of peripheral edema in congestive heart failure.

TABLE 1

Case Number	During Heart Failure				After Compensation			
	Venous Pressure*	Capillary Pressure*			Venous Pressure*	Capillary Pressure*		
		Arteriolar Limb	Summit of Loop	Venous Limb		Arteriolar Limb	Summit of Loop	Venous Limb
1	12	..	..	25	5	30	18	12
2	10	..	..	35				
3	24	..	..	31				
4	10	..	..	25				
5	27	..	..	35				
6	..	..	..	25	..	30	18	24
7	..	..	..	30	..	..	..	15
8	..	..	..	20	..	35	24	11

* All measurements were in mm. Hg.

The evidence that increased pressure within the capillary system in heart failure may force fluid from the circulating stream into the tissues seems well founded. It is necessary then to examine the evidence for the opposing (colloid osmotic) force.

Plasma Proteins. It has been repeatedly emphasized that the plasma proteins, particularly the albumin fraction, constitute the principal osmotically active material in the blood.[19,30,31] Under ordinary conditions these substances exert an osmotic tension of about 25 mm. Hg. Evidence indicates that the colloid osmotic pressure is frequently low in patients with cardiac failure.[14,31,58,64,66,78] Under such conditions the lowered osmotic tension is in synergism with elevated capillary pressure to provoke augmented transudation. Several factors appear to contribute to a decrease in plasma protein during heart failure: (1) inadequate protein intake; (2) deficient absorption from a congested intestinal mucosa; (3) excessive protein loss in the urine and in ascitic and pleural fluids and (4) faulty synthesis of protein by the liver.[19,31,69] Although the plasma proteins may be low in some cases of chronic heart failure, hypoproteinemia is frequently absent.[19,31] It appears that the depletion of plasma protein is rarely sufficient to be the sole factor in edema formation but quite probably it is accessory in some instances.

The Permeability of Capillaries. The early studies of edema formation in heart failure indicated that the integrity of the capillary wall is of considerable importance.[6,70,71] Smirk[70] studied the problem in a group of normal subjects and in patients with congestive heart failure. Pneumatic cuffs were placed about the extremities; when these were inflated to a pressure equivalent to 20 cm. of water higher than the colloid osmotic pressure of the plasma, edema of the extremities occurred. The degree of volume increase of the extremities was

measured with a plethysmograph. He noted that a significantly greater rate of swelling occurred in the extremities of heart failure subjects. For instance, the average increase in hand volume expressed in cc. per 100 cc. of hand per five-hour period was 5.7 in normal subjects and 11.4 in patients with congestive heart failure. However, the possibility remains that the cardiac patients may have had occult edema when the experiment was performed; venous obstruction then may have brought the edema rapidly to a clinical level.

Several explanations have been offered for the capillary changes leading to increased permeability. Loeb[47] and others[19,57] adduced evidence that venous stasis, accompanying venous hypertension, increases the permeability of capillary walls. Some observers[6,19] have suggested that faulty nutrition of the capillary wall, resulting from slow blood flow, causes damage to the vessel. This idea is attractive but has been difficult to prove. Krogh[39] advanced the hypothesis that in certain conditions, capillary dilatation (under the impact of venous engorgement from heart failure[57]) leads to an increase in capillary permeability. This possibility was not borne out by the studies of Landis.[41] Furthermore, Fahr and Ershler[15,16] found that capillaries in patients with heart failure could be twice their normal size without edema formation.

Of particular interest concerning the pathogenesis of capillary changes are the outstanding experiments of Landis.[42] Using microcannulization technics, he showed that the capillaries of the frog mesentery are rendered permeable to fluid and protein by oxygen lack. Such a "protein leak" by the capillaries was demonstrable within a matter of minutes after oxygen deprivation. The process was found to be readily reversible unless capillary damage was allowed to become severe. This observation suggested that anoxemia may form the basis for increased capillary permeability during heart failure. Altschule[1] maintained that a decrease in cardiac output leads to anoxemia and that low oxygen saturation of the blood causes an increase in capillary permeability. Clinical observations supporting this hypothesis indicate that some edematous cardiac patients respond to the administration of oxygen with profuse diuresis only to regain edema when deprived of oxygen.[3,63] Indeed, Drinker[10] has emphasized the rôle of anoxemia of pulmonary capillaries in producing pulmonary edema in myocardial decompensation as well as in other conditions.

The rôle of anoxemia in the production of edema has been disputed by several workers.[15,16,81] For example, in congenital heart disease of the cyanotic type, a marked reduction in the oxygen content of the blood may be present for years without the occurrence of edema.[16] Furthermore, patients with cardiac decompensation frequently develop edema without a marked reduction of oxygen content of the blood.[16]

It has been argued that if increased capillary permeability is present, the edema fluid will contain large amounts of protein.[81] Repeated investigations[8,83] have shown that the protein content of cardiac edema fluid is low, usually less than 0.5 Gm. per cent. Warren and Stead[83] measured the protein content of edema fluid in cardiac patients before and after compensation and found no significant change. The low protein content of edema fluid in patients with heart failure, with severe emphysema and with long-standing anoxemia, has been cited as evidence that pronounced oxygen desaturation of the blood does not increase capillary permeability.[81] None of these data, however, are conclusive. A large amount of protein may pass into the extracellular fluid and the protein concentration may conceivably remain constant if enough water also enters the tissue spaces.

The evidence regarding the rôle of capillary permeability in the pathogenesis of cardiac edema is at the present time both inconclusive and conflicting.

Lymph Flow. Early workers suggested that lymphatic return is increased in the course of cardiac failure.[7] However, McMaster[51] has reported the occurrence of

lymphatic stasis in cardiac patients. He suggested that retardation in the flow of lymph resulted from dilatation and valvular incompetence of the lymphatic vessels themselves. In the same connection, it must be considered that the lymph channels empty into the systemic veins and that an elevation of venous pressure may impair the escape of lymph from these channels.[30] From the experimental evidence at hand, however, it appears that lymphatic obstruction in cardiac patients is the least important of these many possible factors concerned in edema formation. The extracellular fluid resulting from lymphatic blockage is high in protein content.[11] The finding of lowered protein content of cardiac edema fluid, therefore, constitutes the main body of evidence against the importance of lymphatic obstruction in circulatory failure.

Endocrine Factors. Endocrine imbalance as a cause of salt retention should be considered although its importance in edema formation is still not clear. Evidence that salt retention is directly correlated with an increase in certain steroid hormones was found by Thorn and Emerson.[79] They demonstrated a premenstrual retention of salt and water. During and following the menstrual period salt was excreted in excessive amounts and water was lost with it.

Adrenocortical hormones have been known for many years to be concerned with salt metabolism of the kidney. According to Raab,[59] certain adrenocortical hormones are greatly increased during congestive heart failure. His studies indicate the need for a thorough investigation of the effect of hormones secreted by the adrenal cortex in heart failure.

Since some patients with cardiac insufficiency and edema failed to have a normal diuretic response to ingestion of water, Fremont-Smith[21,22] postulated an increased secretion of the antidiuretic factor by the posterior pituitary gland. Recent studies by Ralli et al.[60] on the mechanism of ascites in cirrhosis of the liver offer another explanation for the apparent increase in the antidiuretic factor. The amount of the antidiuretic factor normally inactivated by the liver is greatly decreased as a result of impaired liver function.[60] In cases of cardiac decompensation with long-standing congestion of the liver, the antidiuretic factor may not be destroyed and, consequently, may play a part in water retention. Investigation of the rôle of the antidiuretic factor in the pathogenesis of cardiac edema may prove productive.

SUMMARY AND CONCLUSIONS

1. Evidence concerning the rôle of the principal factors thought to be involved in the pathogenesis of peripheral cardiac edema has been presented.

2. Studies of cardiac output do not show a consistent decrease in this function; however, the data indicate a definite trend toward a low cardiac output during congestive heart failure.

3. There is considerable evidence that renal function is impaired during cardiac decompensation so that salt and water are retained by the kidneys. Sodium chloride and water retention is accompanied by abnormal water storage in the extracellular tissues and thence edema formation. Glomerular filtration and renal blood flow have been reported to be markedly decreased during heart failure; decreased glomerular filtration has been offered as a likely mechanism for salt retention. Renin, which has been found to be increased in renal venous blood of patients with cardiac failure, may be causally related to functional changes in the kidney but this relationship is not clear.

4. One of the most interesting features of the mechanism of edema formation is the problem of the pathogenesis of venous hypertension. The conceptions of "backward failure" and "forward failure" have been contrasted in some detail. At present, the evidence does not permit of a conclusive answer to the cause of elevated venous tension in heart failure.

5. When the venous pressure is elevated during cardiac decompensation, it plays a part in edema formation. An increase in capillary pressure is present and transuda-

tion of fluid into the extracellular tissues occurs.

6. Plasma proteins are sometimes low in patients with cardiac failure. When they are below a certain critical level, the lowered osmotic pressure may act as an accessory factor in the formation of edema.

7. It has been suggested that adrenocortical and posterior pituitary function may be disturbed during congestive heart failure but there is, as yet, no satisfactory evidence in support of this hypothesis.

8. The evidence is insufficient to warrant the conclusion that increased capillary permeability and partial lymphatic obstruction are major considerations in the pathogenesis of edema.

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Seminars on Thromboembolism

Use of Anticoagulants in the Treatment of Heart Disease*

With Special Reference to Coronary Thrombosis, Rheumatic Heart Disease with Thromboembolic Complications and Subacute Bacterial Endocarditis

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INVESTIGATION regarding the possible value of anticoagulants in the treatment of thromboembolic phenomena continues to appear logical and, indeed, imperative because of the following facts:

1. Thromboembolic phenomena cause the terminal fatal episode in the lives of more persons over fifty than any other pathologic mechanism.

2. A large percentage of these patients suffering from thrombi or emboli in the vessels of the brain, the heart, the kidneys, the legs, or elsewhere, do not or would not die from the effects of the original thrombus or embolus. Death results far more frequently from subsequent developments including: (a) propagation of the thrombus to block off additional arteries or veins which are strategically located so that they interfere with the vital function of the organ supplied; (b) the dislodging of emboli from the original thrombus which, when transported by the blood currents, lodge at critical points interfering with the blood flow and producing serious disturbances of the local tissues, or, in the event of emboli of sufficient size lodging in the heart, the pulmonary or the cerebral circuit, producing sudden death; (c) the development of secondary thrombi which may in turn give off emboli. Examples of this type of process are represented by mural thrombi with coronary infarction and thrombi in the veins of the legs upon prolonged bed rest.

3. Experience has demonstrated that if a patient survives a first attack of thrombosis, or a first embolus, or indeed a subsequent attack, he may live for many months or even years. It is, therefore, incumbent upon us to do everything in our power to bring about survival through each individual attack.

4. Interruption of the thromboembolic process presents a logical approach to the problem. Our former methods of treatment of these thromboembolic phenomena have never been aimed at modifying the fundamental process involved. Frequently, as in the instances of coronary thrombosis or auricular fibrillation with heart failure, the combination of complete rest, restriction of fluids, sedation and mercurial diuretics have all encouraged further thrombosis either in the vessels, the chambers of the heart or in the veins elsewhere.[1] The effects of the xanthines, especially aminophylline[2,3] and digitalins[4] have been challenged in this regard. Work in our laboratory and elsewhere seems to exonerate aminophylline. As much as 1.8 Gm. given daily has failed to change

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the prothrombin time even while producing toxic phenomena. Frequently penicillin is used in the presence of thromboembolic episodes. It has recently been shown to increase markedly the thrombosing tendency both as to rapidity of formation and the firmness of the clot.[5,6] This apparently holds also for streptomycin.[7]

5. It has seemed, therefore, that serious study must be given this problem. Fortunately, two agents are available, either of which apparently can interrupt the thromboembolic process under certain favorable conditions. It is the purpose of this article, therefore, to review the present status of the use of these substances, heparin and dicumarol, particularly in reference to diseases affecting the heart.

The era of intensive study with anticoagulants really began in 1916 when J. McLean,[8] a student of William H. Howell, discovered heparin as a by-product of another investigation. Its anticoagulant properties were recognized with the initial experiment, and from that time forth Howell and other investigators have carried on many studies regarding the properties of this substance.[9] As early as April 7, 1917, Howell, in a Harvey Lecture,[10] expressed the hope that this or a related substance would find "a suitable application in experimental work, and possibly in the therapeutic treatment of disorders of coagulation." Early preparations, however, were not satisfactory for therapeutic use in man. Considerable work was carried on in the laboratories at John Hopkins[11,12] and also at the Connaught Laboratories at the University of Toronto under Best.[13,16] Later investigators, including Jorpes,[17,18,19] continued investigations at the Karolinska Institut of Stockholm. Details of the discovery and the chemistry of heparin have recently been reviewed by Jorpes in his monograph on this subject.[20]

A provisional international heparin standard was defined by the Department of Biological Standards of the National Institute for Medical Research in London in November, 1942. A water-free sodium salt of heparin obtained from a "crystalline barium salt," supplied by the Connaught Laboratories of the University of Toronto, was selected as standard. It contained 130 Toronto Units per mg., thus approximating the strength of the strongest sodium salts of heparin from ox liver, or 160 per cent of the strength of the Swedish standard heparin.[21] This difference in strength between the heparin prepared on the basis of the International Standard (which is that commonly used in this country) and the heparin prepared on the basis of the Swedish Standard must be borne in mind when interpreting the reports on the use of heparin in the Swedish literature. In other words, in terms of milligrams, the dose of heparin utilized in Sweden today averages approximately one-third or more higher than that necessary to produce the same therapeutic effects in terms of the heparin used in this country. This is frequently not realized by American physicians and may, if neglected, result in some unfortunate complications.

The exact mechanism of the action of heparin is not clearly understood. It appears that the activity of heparin is dependent on, or at least accentuated by, the presence of the serum proteins, especially a fraction of the serum albumins, and that it takes place largely on the prothrombin rather than on the activated thrombin. It is not clear whether this reaction is direct or indirect. A prominent feature of the reaction mechanism of heparin is the mutually neutralizing effect of heparin and thrombokinase. Some studies have been carried out on the significance of electric charges on the heparin effect. It has a high molecular weight and carries an exceptionally large surface charge, apparently the largest of all the organic compounds of the animal body. The strongest preparations consist of up to no less than 45 per cent sulfuric acid. The strongest

compounds of a similar nature hitherto known, "the nucleic acids," contain only 25 per cent of phosphoric acid. The anticoagulant activity apparently increases with increasing sulfur content. Jorpes concludes that the increase in sulfur causes a greater increase in activity if introduced into the highly esterified samples, thus indicating that it is the abundance of biontic charges that makes the polysaccharide an anticoagulant.[20] Jorpes and his co-workers have demonstrated that the source of the formation of heparin, or at least its storage in the body, is to be found in the Ehrlich mast cells or heparinocytes which are found along the sides of the minute vessels, probably throughout the body, but in higher concentration in the subcutaneous and lung tissues.[20] Free and active exchange of fluid through the walls of the capillaries appears to be the means by which heparin is carried from these cells into the lumina of the vessels.[22] A method of administration of additional heparin for clinical purposes will be described in detail later in this paper.

The second anticoagulant of great importance was described, isolated and synthesized by Link and his co-workers in a now historic series of studies at the University of Wisconsin.[22–26] This preparation is known as dicumarol (3,3′methylene-bis-(4-hydroxycoumarin)). It was first isolated from spoiled sweet clover and later synthesized from coal tar derivatives and has been shown to have a definite anticoagulant property. The exact mechanism of its action, like that of heparin, is not entirely established at this time but it is believed to be on the basis of an inhibition of the production of prothrombin by the liver. Shortly after the description of dicumarol and its chemical and anticoagulant properties by Link and his co-workers, three groups, Bingham, Meyer and Pohle[27] of the University of Wisconsin, Butt, Allen and Bollman[28,29] of the Mayo Clinic, and Prandoni and Wright[30,31] of New York, undertook clinical investigations of the use of dicumarol in human beings, especially as it related to thrombophlebitis. Since that time it has been conclusively demonstrated by the work of these authors and others, notably Barker[32] of the Mayo Clinic in this country, and Swedish investigators including Bruzellius[33] and Zilliacus,[34] that dicumarol exerts a favorable effect on the course of thrombophlebitis and the thromboembolic complications of that group of diseases. It has also been demonstrated to be of great value as a prophylactic measure in the prevention of postoperative emboli and thrombophlebitis.

The action, as indicated above, is not completely clear, but the following factors apparently play a part: (1) A decrease in the prothrombin activity. (2) A prolongation of the coagulation time. This factor is not always clearly demonstrated by the use of the Lee-White method for the study of coagulation time, but by using lusteroid tubes and paraffin-lined tubes, Kadish[35] and Vander Meer, Newman and Wright[36] have demonstrated that there is a prolongation of the coagulation time in dicumarolized patients. (3) A decrease in the thrombosing tendency has been demonstrated in various forms of neutral vascular tubing.[37] (4) There is a marked decrease in the thrombosing tendency following sodium morrhuate injections in dicumarolized patients.[37] (5) There is some evidence which suggests a decrease in the adhesiveness of platelets in the presence of dicumarol.[37] (6) There is evidence accumulating which suggests an increase in the antithrombin components or activity in the blood in dicumarolized patients.[37]

The effects of heparin in terms of therapeutic results are very similar to those of dicumarol except that heparin acts more rapidly and therefore may be a valuable aid in the treatment of patients in whom rapid results are desired. Heparin is some-

what more difficult to administer in that it requires either continuous intravenous injections or a number of intramuscular or intravenous injections per day, or lastly it may be used with a retarding base, such as the Pitkin menstruum. When injected subcutaneously or intramuscularly the original preparations in the Pitkin menstruum produced pain and other local and general side effects. More recent modifications of these preparations are less objectionable in these regards but are still quite painful. We have not as yet had the opportunity of studying the other by-effects in detail.

Dicumarol is slower to act than heparin, requiring approximately thirty-six to forty-eight hours to manifest its activity, but since it is given orally it is easier to administer. Apart from the risk of hemorrhage from overdosage, it does not customarily produce any untoward effects such as digestive disturbances or reactions of hypersensitivity. There have been no definite examples of either of these latter reactions attributable to the drug in more than 800 patients treated with dicumarol under the author's observation. The use of dicumarol is accompanied by the difficulties inherent in the present prothrombin tests. Even the most sensitive coagulation time tests[35,36] do not follow the prothrombin activity closely enough to be satisfactory for the control of dicumarol therapy; therefore, prothrombin activity tests must be used. The methods available today are not suitable for use except by a skilled technician and certainly the patient cannot control his own dosage. At the present writing the major obstacle preventing widespread use of dicumarol is the lack of a simple but accurate test for the determination of prothrombin activity in man.

TECHNIC FOR CLINICAL ADMINISTRATION OF DICUMAROL

The following routine for the administration of dicumarol has been found to be therapeutically satisfactory and safe. Having made certain that there are no contraindications to its use such as recent hemorrhage, blood dyscrasias with bleeding tendencies, active ulcers, hemorrhagic ulcerative colitis, etc., and with the first prothrombin time within normal range, 300 mg. of dicumarol is given in a single dose. Each morning the prothrombin time is determined and the dose for that day is decided upon after the result of the test has been received. Either 200 mg. or 100 mg. is given daily until a prothrombin time of 30 seconds is reached after which 100 mg. is given daily until the prothrombin time equals 35 seconds or more. Thereafter no dicumarol is given until the prothrombin time returns to under 30 seconds when again 100 or 200 mg. are given until a level of 35 seconds or more is reached. The objective should be to keep the blood at the therapeutic level of 30 to 50 seconds during active hospital treatment, and between 25 and 35 seconds during ambulatory treatment. If the prothrombin time rises to 60 seconds or more, or if hemorrhagic manifestations occur in the skin, mucous membranes, urine or stool, dicumarol is discontinued and vitamin K is given intravenously, 64 to 72 mg. once and repeated in four hours. Usually this will suffice to reduce the prothrombin time to safe limits within twelve to twenty-four hours; if not, fresh whole blood transfusions, one or two of 300 to 500 cc. each, will solve this problem. In 800 cases we have not had a death from dicumarol bleeding with the doubtful exception of one complicated case described later in this paper. Transfusions have been found necessary in only two of the last 200 patients treated.

IF HEPARIN IS TO BE USED, THE FOLLOWING STANDARDIZED PROCEDURES FOR THE USE OF HEPARIN ARE SUGGESTED

I. *Intermittent Dose Method.* (1) An initial clotting time of the whole blood in glass tubes should be performed before heparin is given. We recommend the Lee-White modification of the Howell method which, although crude, still appears to be the most practical test. It is performed as follows:* "One ml. of blood is withdrawn from the arm vein, using a small all-

* *Am. J. M. Sc.*, 145: 495, 1913.

glass syringe. The time at which the blood is drawn is noted. The needle is removed and the syringe then emptied into a small glass tube (Widal tube) about 8 mm. in diameter, which has previously been rinsed out with physiologic saline solution (.85 per cent). The tube is rotated endwise (tilted) every 30 seconds and that point at which the blood no longer flows from its position, but maintains its surface contour when inverted, is taken as the endpoint. Care must be used to exclude air bubbles, as they tend to accelerate coagulation . . . If the test is done at room temperature (65°–90°F.), the error, although present, is within one minute and may be neglected . . . Normal coagulation time is 6½ minutes (5–8 minutes)." At present coagulation times should be done in glass tubes. In extensive tests at The New York Hospital on the clotting times of whole blood in paraffin-lined and lusteroid tubes, in untreated as well as treated patients, we have observed a wide range of variation in the clotting times in paraffin-lined and lusteroid tubes. This makes their use unsuitable for this type of study and they cannot be recommended at present. Further studies are being carried out.*

2. Fifty mg. of heparin in 50 to 100 ml. of physiologic saline are then given slowly by vein.

3. Clotting times should be done fifteen minutes and two and one-half hours after the administration of heparin. If the clotting time at two and one-half hours falls below fifteen minutes, give 75 mg. of heparin for subsequent doses. After a few trial studies the selected safe therapeutic dosage may be continued without repeating the clotting times routinely. The check of one series each day is a safety factor.

4. The dosage schedule may vary from patient to patient according to the clotting times. In general, injections of 50 to 75 mg. of heparin are given every three or four hours and are continued for two days. (This is the method used by the Swedish workers in a large series of cases of thrombophlebitis. As previously mentioned, the dosage recommended by them should not be used in this country since the temporary International Standard for heparin, used in the United States, is 160 per cent of the strength of the Swedish standard heparin.)

5. The dicumarol dosage plan is the same whether or not heparin is used and 300 mg. should be given concurrently with the first dose of heparin. Prothrombin times should be done every day on blood taken just *before* a dose of heparin is due, since large amounts of heparin in the circulating blood may affect the prothrombin determination.

II. *Continuous Intravenous Drip Method.* Some physicians may prefer the continuous intravenous method to the intermittent injection method. Accurate measurement of the prothrombin time to determine dicumarol dosage can be accomplished with this method only by slowing the drip from 5 to 8 drops per minute because the heparin interferes with the coagulation of the plasma used in the test. (It has not been proven that heparin has no antiprothrombin action.[20]) If the continuous intravenous method is used, it is recommended that 300 mg. of heparin be put in 1,000 ml. of 5 per cent glucose and allowed to run into the vein at approximately 25 drops per minute for twenty-four hours. Clotting times should be done every two hours, otherwise trouble may be anticipated. The clotting time should be kept between 20 and 40 minutes. The total daily dosage necessary for this may vary considerably. The infusion needle should be firmly fixed in place. The veins of the backs of the hands or dorsal surfaces of the feet have been found to be the most satisfactory. Heparin given in this fashion may usually be discontinued after from twenty-four to forty-eight hours. Three hundred mg. of dicumarol may be given the first day. Four hours after the heparin infusion has been stopped, blood should be drawn for the prothrombin test and dicumarol dosage determined thereafter accordingly.

III. Due to local pain and other side effects, the original experimental preparations in the Pitkin menstruum were not suitable for general use. Even the more recent preparations are very painful.

TECHNIC FOR PROTHROMBIN ACTIVITY DETERMINATIONS

Most workers have used either the Quick test[38] or the Link-Shapiro modification of the Quick

* Vander Meer, R., Newman, A. and Wright, I. S. Unpublished data.

test[24,39,40] for determining the plasma prothrombin. The Link-Shapiro modification of the Quick test which has been found to be satisfactory is performed in our laboratory as follows:

The reagents used are:

(1) 0.1 M sodium oxalate, prepared by dissolving 13.4 Gm. of anhydrous, reagent grade sodium oxalate in 1,000 ml. of distilled water; (2) 0.85 per cent sodium chloride, prepared by dissolving 8.5 Gm. of reagent grade sodium chloride in 1,000 ml. of distilled water; (3) 0.025 M calcium chloride, prepared by dissolving 2.77 Gm. of anhydrous, reagent grade calcium chloride in 1,000 ml. of distilled water; and (4) thromboplastin-calcium chloride mixture, prepared as follows: 2.5 ml. of 0.85 per cent sodium chloride is added to 50 mg. Maltine thromboplastin in a small centrifuge tube. It is stirred until a uniform suspension is obtained and the suspension is then kept (with constant stirring) at 54°–55°C. in a water bath for ten minutes. When the suspension has been cooled to 25°–26°C., 2.5 ml. of 0.025 M calcium chloride solution is added and the mixture stirred for four minutes. After centrifugation at 1,700 r.p.m. for four minutes, the tube is removed from the centrifuge, taking care not to stir up the packed sediment, and the slightly turbid supernatant fluid is pipetted off to be used in the determination. (Note: Ampules of thromboplastin should be stored in the icebox.)

The necessary apparatus includes:

(1) A 37.5°C. constant temperature water bath (Machlett No. 84–410 metal constant temperature water bath, or A.H.T. No. 9925-A glass constant temperature water bath); (2) 100 by 12 mm. test tubes; (3) copper test tube racks (Army medical type to hold 100 by 12 mm. test tubes); (4) stopwatch; (5) Folin-Wu micro sugar pipettes (Normax), graduated to contain 0.1 and 0.2 ml.; and (6) Kahn viewer (if the Machlette No. A84–410 type water bath is used).

In performing the test, blood samples are taken by mixing 4.5 ml. blood quickly with 0.5 ml. of 0.1 M sodium oxalate. The oxalated blood is centrifuged at 1,700 r.p.m. for ten minutes and the clear plasma is transferred with a pipette to a test tube. Clotting time should be determined at once, but if stored in a refrigerator the plasma will remain stable for several hours. If prothrombin times are to be done on 12.5 per cent diluted plasma as well as on whole plasma, such a dilution can be made in another 100 by 12 mm. tube by diluting 0.1 ml. of whole plasma with 0.7 ml. of 0.85 per cent saline. This should be mixed by tapping the lower end of the tube.

Two tenths ml. portions of thromboplastin-calcium chloride suspension are transferred into 100 by 12 mm. test tubes with a 0.2 ml. micro blood sugar pipette and these tubes are placed in a rack along with the test tubes containing whole plasma or its dilution. The rack is then placed in a 37.5°C. constant temperature water bath. When the contents of the tubes have reached the bath temperature (usually 60 seconds), 0.1 ml. of whole or diluted plasma is transferred with a micro blood sugar pipette to a tube containing 0.2 ml. of thromboplastin-calcium chloride suspension. The plasma is quickly blown into the thromboplastin mixture while, at the same time, the stopwatch is started. The tube is tapped sharply to mix the solutions and a small nichrome wire stirrer is introduced to stir the solution at such a rate that the wire sweeps across the test tube from one side to the other two times per second. The process of stirring may take place outside of the water bath and viewed under the magnifying glass of a Kahn viewer. The end point, which is the formation of a fibrin clot, is that point at which the fibrin clot is sufficiently stable to be drawn to one side by the stirrer, thus bringing to view a clear area. The clot is usually turbid since the calcium oxalate formed upon calcifying the oxalated plasma is enmeshed in the clot. The prothrombin clotting time is the time in seconds required to form a clot; normal standards are for whole plasma, 13 to 17 seconds; for 12.5 per cent diluted plasma, 35 to 42 seconds.

If a constant temperature water bath with glass walls is used, the clot formation can be viewed through the glass walls of the bath and a Kahn viewer is not essential. However, in our laboratory a Kahn viewer is preferred because thin clots, such as those obtained with 12.5 per cent diluted plasma, are obtained easily and quickly.

Findings resulting from this test are reported in terms of seconds or they may be translated into per cent of prothrombin activity. The normal results with whole plasma fall within a range of from 13 to 17 seconds. Slight therapeutic effectiveness may begin in some patients at approximately 23 to 25 seconds and become increasingly active as the time is prolonged. Thirty seconds and 35 seconds are key levels in regard to dosage. We endeavor to maintain a level of between 30 and 50 seconds to get maximum therapeutic effects without toxicity. Some workers, including Barker,[32] believe that reports of these tests should be rendered in terms of percentage of prothrombin activity of normal plasma. When and if this can be standardized by the workers in this field it may be desirable, because it permits a correction for the use of thromboplastin of various strengths. At present, however, there are at least three different methods of setting up such curves in use in different institutions in this country. Therefore, reporting in percentage under these conditions may result in misinterpretation by other workers. The most correct technic uses a curve produced as the result of the dilution of normal plasma with prothrombin-free plasma so that 90 per cent, 80 per cent, etc., down to 10 per cent solutions of normal plasma are obtained and prothrombin tests performed on these various diluted samples. A curve can thus be plotted which will indicate prothrombin times for various percentage levels of prothrombin deficiency. This is a logarithmic curve, not a straight line. For example, the first few seconds' increase in the prothrombin time indicates a great decrease in the prothrombin percentage of normal. When the deficiency becomes marked, many seconds' increase may mean a difference of only a few per cent in the concentration of prothrombin. As Barker points out, "by plotting a dilution curve as above outlined, any worker using a thromboplastin of unknown potency can determine a set of prothrombin times for that thromboplastic substance which indicate various percentages of prothrombin deficiency and, if certain prothrombin percentages are considered important levels, he can easily determine their equivalents in prothrombin times." In order to continue this it is necessary either to use only new thromboplastins which give identical results with the old, or to run relatively large samplings from so-called normals to establish a new curve with each new batch of thromboplastin.

The establishment of such a curve does not eliminate factors of error which have occurred in the prothrombin determinations and, in fact, it may actually magnify them. At present, following the technic of Russ, we are using Lyovac (dried plasma) prepared for this purpose as our standard control. It is used in the dilution of 12.5 per cent against the plasma of a similar dilution and gives standard results for that dilution of approximately 35 to 40 seconds.[41,42]

A more serious problem, pointed out above, lies in the use by certain institutions at present of straight curves. In other words, if the normal control for whole plasma is 15 seconds, and the result of the patient's test is 30 seconds, this is considered to be 50 per cent of normal, a figure far different from that obtained on the logarithmic curve above described. A third technic which is unjustified has been found in use in certain institutions where, instead of 50 per cent, the same figures, namely, 15 per cent for the normal standard and 30 per cent for the patient, would be interpreted as 200 per cent. This may give rise to serious misunderstandings and at present appears to be safeguarded against by the use of reference to seconds and by standardizing the basic technic to the greatest degree possible.

Studies have been carried on in our laboratory at The New York Hospital regarding the effects of food and exercise on prothrombin times.[43] These studies were undertaken to investigate: (1) The daily variation in prothrombin activity of normal individuals; (2) to determine if the time of day that blood samples were taken affected the prothrombin activity; (3) to ascertain the effect of exercise on prothrombin activity and (4) to study the effect of high cholesterol intake on the prothrombin determination. In these studies we used the one step method of Quick. Plasma prothrombin times were measured on both whole (100 per cent) and diluted (12.5 per cent) plasma.

Diurnal prothrombin time determinations were investigated in twenty normal individuals

over a period of four to ten weeks. An average of 15.4 seconds (90 per cent of the values obtained are within the range 15.4 ± 1.5 seconds) was obtained as the prothrombin time of 625 determinations on whole plasma. The average prothrombin time in 627 determinations of 12.5 per cent plasma was 38.4 seconds (75 per cent of the values obtained are within range 38.4 ± 3 seconds).

In order to determine if the time of day had any effect on prothrombin activity, blood samples were taken before breakfast, before lunch and after lunch on nine different individuals over a period of three weeks. One hundred prothrombin determinations were made on blood samples taken before breakfast. The average prothrombin time of 100 per cent plasma was 15.0 seconds; that for 12.5 per cent plasma was 35.4 seconds. Before lunch the average value for 109 determinations was 15.1 seconds for 100 per cent plasma and 39.4 seconds for 12.5 per cent plasma. After lunch the average was 14.5 seconds for 100 per cent plasma and 37.5 seconds for 12.5 per cent plasma for 115 prothrombin determinations.

The effect of a short period of strenuous exercise on prothrombin activity was also studied in ten normal students. Blood samples were taken, and the students then ran down and up four flights of stairs, following which blood samples were taken again. Before exercise, thirty-five determinations were made. The average was 16.7 seconds and 39.9 seconds for 100 per cent and 12.5 per cent plasma, respectively. After exercise, an average of 16.6 seconds and 39.9 seconds on 100 per cent and 12.5 per cent plasma, respectively, was obtained in thirty-four determinations.

To ascertain if ingestion of a high cholesterol diet would affect the prothrombin activity, four normal individuals were given six eggs a day besides their usual meals and their prothrombin measured daily over a period of four weeks. The average of sixty-seven determinations on 100 per cent plasma and 12.5 per cent plasma was 16.1 seconds and 40.1 seconds, respectively.

The results of these studies indicate that although slight variations are obtained these are within the experimental error of the method. If any of these factors, such as the time of day that blood samples are taken, exercise or high cholesterol intake, do affect the prothrombin activity, the changes are of minor significance. Therefore, prothrombin determinations may be made at various times of the day after exercise and in patients on a high cholesterol diet. They will be satisfactory for guiding dicumarol therapy unless other factors interfere.

CLINICAL EXPERIENCES WITH ANTICOAGULANTS IN THE TREATMENT OF THROMBOPHLEBITIS

The results following the use of dicumarol and heparin, given separately or in combination, in the treatment of thrombophlebitis have been so remarkable that investigation of the use of anticoagulants in other diseases is justified. Figures on large series reported by Barker and co-workers,[32] Bruzelius,[33] Jorpes,[20] Zilliacus[34] and by our own group[44] clearly indicate that the use of anticoagulants constitutes the most important forward step in the treatment of thrombophlebitis. It is interesting that almost identical results were being obtained in Sweden and in this country although communication was markedly inhibited during the war years.

INCIDENCE OF THROMBOEMBOLIC COMPLICATIONS OF MYOCARDIAL INFARCTION

The importance of thromboembolic complications of coronary thrombosis with myocardial infarction has long been recognized. In 1937, Blumer[45] reported 943 cases of myocardial infarction in 132 of which clinically detectable emboli or thrombi were found. Hellerstein and Martin[46] have recently reviewed the literature and have added 655 cases from later reports. The incidence of clinically detectable thromboembolic lesions for the entire group was 11.5 per cent. In their autopsy series of 160 cases of myocardial infarction, however, 73 (45 per cent) had a total of 111 peripheral thromboembolic episodes. These peripheral complications were a main or contributory

cause of death in 43 of the 160 cases. Master and his associates[47] have stated that in patients under fifty the most common cause of death associated with myocardial infarction is arterial embolism. Nay and Barnes[48] reported embolic or thrombotic complications in 37 of 100 consecutive cases of acute myocardial infarction encountered in the Mayo Clinic. In these thirty-seven patients there were a total of forty-eight thromboembolic complications, and these complications were an important contributing factor in the death of twelve patients.

ANIMAL STUDIES WITH ANTICOAGULANTS IN CORONARY THROMBOSIS AND MURAL THROMBI

The recognition of the occurrence of such thromboembolic complications of coronary thrombosis and other heart disease led early workers to speculate on the possibility of anticoagulant therapy in these conditions. Solandt and Best,[49] in 1938 reported experiments in which coronary thrombosis was produced by isolating the coronary artery and injecting sodium ricinoleate within the lumen. This material was kept in contact with the intima for five minutes and clamps on the vessel were then released. In almost every case in which no heparin was used thrombosis was present; whereas in the heparinized series this was almost never observed. Solandt, Nassim and Best[50] continued their studies with the production of cardiac mural thrombi, and the prevention of their formation by the administration of heparin. A technic was evolved by which large mural thrombi could be regularly produced in the lumen of the left ventricle. The endocardium of this cavity was injured by injecting sodium ricinoleate, and the myocardium was damaged by ligating the anterior descending branch of the left coronary artery. Without heparin there was rapid formation of a thrombus but none was seen in those experiments in which heparin was given well before the injury was produced. The results of their experiments left no doubt that under certain experimental conditions the effect of heparin in preventing thrombosis could be readily demonstrated. Following these studies sporadic efforts were made to use heparin in the treatment of coronary thrombosis, but as far as is known no large well controlled series were run, largely because of the difficulties of continued heparinization. The question of increasing the hemorrhage in the intima was also raised, more as a theoretical than as a proven risk. Following the early clinical use of dicumarol a few patients with coronary thrombosis with myocardial infarction were treated with it. The author treated his first patient with thrombophlebitis in May, 1942.

CLINICAL EXPERIENCE WITH THE USE OF ANTICOAGULANTS FOR THE TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

It is difficult to evaluate the effectiveness of anticoagulant therapy in a particular patient who has suffered from an uncomplicated attack of coronary thrombosis in its early stages, since at present we are unable to predict with certainty which patient will have a rapid series of secondary episodes of thrombosis, which will have one or more embolic phenomena, and which patient will prove to have an uneventful recovery from the immediate attack. The patient who has had a series of episodes of thrombosis in different radicals of the coronary tree within a short period of time, and with evidence of multiple myocardial infarctions following these, or whose original thrombus propagates centrally thus blocking off additional branches of the same coronary artery and producing a much larger area of myocardial infarction, has an increasingly serious prognosis with each episode or extension. Once a

person has more than two episodes of thrombosis within a pericd of two or three weeks there is an increasing likelihccd that further episodes will follow and the outlook is progressively poorer. In like manner, once a patient has developed a mural thrombus and has suffered one or more embolic phenomena, either pulmonary or peripheral, the prognosis is grave although some individuals do survive such episodes. It has been the lot of all cardiologists to care for many patients through such a course, helpless to prevent the repeated complications of thromboembolism and to avert death. In fact, as previously pointed out, the regimens which include complete rest, the rather free use of narcotics or other sedatives, and, when indicated, the use of mercurial diuretics, encourage the production of additional thrombosis, the very thing which is, in another sense, being combated. In spite of the difficulty of evaluating the results of such treatment in the individual case with coronary thrombosis, the significant results obtained in the study of thromboses of other types warranted an exhaustive study of this group of cases. In order to put the drug to the most difficult test first, a group of patients who were classified as the "complicated group" were selected on the basis of fulfilling one or more of the following criteria:[53,54]

1. Patients who developed evidence that thrombi had formed in different areas of the coronary tree, or that the original thrombus had propagated. These conclusions were based on evidence either of multiple areas of myocardial infarction or a marked extension of the original area, with characteristic precordial pain, fever, leukocytosis and increased sedimentation rate, and accompanied by definitely confirmatory electrocardiographic findings.

2. Patients who suffered from repeated embolic phenomena either to pulmonary or other areas. (It was recognized that certain of the pulmonary emboli might have arisen in the extracardiac circulation; but following myocardial infarction, the percentage of pulmonary emboli is considerable, and from whatever source, repeated pulmonary emboli have an increasingly serious prognosis.)

3. Patients who developed evidence suggesting that factors one and two were both operative.

Experiences with forty-three such complicated cases and an additional thirty-three patients who had suffered from uncomplicated first or second attacks of coronary thrombosis, making a total of seventy-six patients, were reported in October, 1945, before the California Heart Association.* This series has continued to increase, but has recently been incorporated into a national study of this problem. The figures of this large study have not been completed as yet. Of the first forty-six complicated cases in the original series, forty-one patients ceased having their serial episodes as soon as they were under the effect of dicumarol; eleven died (24 per cent).[53] This mortality is the same as that for coronary thrombosis with myocardial infarction as a whole, but was less than the estimated mortality for these patients (60 per cent plus), who were selected because of the extreme seriousness of their condition. Eight of these died of cardiac failure secondary to their pretreated massive infarctions. Of the thirty-four uncomplicated patients treated, four died (12 per cent). This incidence is lower than the average rate (20 to 30 per cent). A few case histories illustrating the type of patients selected for this form of therapy may be considered to be of interest:

CASE 39. *Multiple thromboses within the coronary arteries with myocardial infarctions:* A fifty year old Army major developed a coronary thrombosis with anterior myocardial infarction. Twelve

* Stanford U. Medical College.

days later, he developed a posterior infarction. Nineteen days later, there was evidence of extension of the posterior infarction. This patient, therefore, was considered to be a complicated case of coronary thrombosis. There was evidence of thrombosis in several areas of the coronary tree and probably extension in one of the areas. At the time that he was seen by the author he was desperately ill, in an oxygen tent, gasping for breath, cyanotic and profusely sweating. His outlook appeared grave. Dicumarol was given for thirty days. There were no further episodes of extension. He made an uneventful recovery and was retired from the Army to return to his civilian home.

CASE 77. *Coronary thrombosis, infarction, mural thrombus and peripheral emboli:* A male, forty-six years of age, also an Army major, had suffered an anterior infarction. On the eighth day he developed an embolism to the right femoral artery; on the tenth day, an embolism to the left femoral artery; and on the twelfth day, a cerebral embolism. He, likewise, was in extremis when seen by the author. It is possible that the embolic phenomena to his legs really constituted a saddle embolus, but this was not clearly established. Despite the bad prognosis, he was started on dicumarol which was continued for thirty days. No further episodes of embolism occurred, and he made a very satisfactory recovery but had residual intermittent claudication of his right calf muscles upon walking three blocks.

CASE 78. *Septal infarction, cerebral and peripheral emboli:* A female, sixty-eight years of age, suffered from hypertension and diabetes of many years' duration, and also had gallbladder disease. She developed a septal myocardial infarction with auricular fibrillation. On the twenty-eighth day she had an embolism to the right femoral artery. On the thirty-first day she had a cerebral embolism which produced hemiparesis and aphasia. She became desperately ill. Dicumarol was started and continued for eighteen days. At that time it was necessary to stop it so that the leg which had meanwhile become necrotic and infected could be amputated. This was done four days after cessation of the dicumarol therapy. She had an uneventful recovery, including recovery of her speech, and is alive at the time of this writing some fifteen months after the above episode. She still continues to have auricular fibrillation.

CASE 21. *Pulmonary infarctions from a mural thrombus; death from heart failure:* A male, forty-two years of age, developed an anterior infarction. On the sixth day he experienced pain in the right lateral chest followed by bloody sputum, and at the same time developed auricular fibrillation. The chest pain was believed to be due to a pulmonary embolism. This was confirmed by an episode on the seventh day with pain in the left base posteriorly. On the ninth day there was a repetition of this type of episode in the right middle lung field. Dicumarol therapy was started. No further emboli occurred. Nevertheless, the patient pursued a downhill course, and died on the thirtieth day, which was after twenty-one days of dicumarol therapy.

At autopsy, he was found to have generalized congestive failure. He had multiple pulmonary infarcts but none appeared to have occurred within two weeks. There was a thrombus in the right coronary artery blocking several branches. In this area the myocardium was necrotic, yellow, fatty and very soft. Attached to the endocardium at this site was an olive-shaped mural thrombus which appeared relatively recent, but was completely sealed over and very smooth. An examination of the patient's veins showed no other likely sources of emboli. It appeared probable that the mural thrombus, which at one time was propagating irregularly and capable of giving off emboli, had become sealed over and smooth following anticoagulant therapy. This could not be proven conclusively. Four additional similar mural thrombi have been seen in later autopsies of treated cases.

Numerous additional cases might be cited in each of the above classes.

PRELIMINARY CONCLUSIONS REGARDING THE USE OF ANTICOAGULANTS IN THE TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

After three and one-half years of study involving eighty patients, the following conclusions seemed warranted:

Dicumarol had not aggravated the condition of any patient. It appeared physiologically sound to give anticoagulant therapy when there was a tendency for (1) propagation of the thrombus, (2) multiple thrombi to form in the coronary arteries or elsewhere and (3) when one or more emboli had occurred. Thromboembolic processes appeared to have been interrupted. There was no evidence that thrombi had been dissolved once they had formed. Progression of established infarctions did not appear to be interrupted by the use of dicumarol. The rate and rhythm of the heart was not directly affected by dicumarol. The risk of future attacks appeared unchanged after dicumarol had been discontinued.

In January, 1946, Nichol and Page[55] described their experiences with dicumarol therapy in acute coronary thrombosis, reporting results in fifty unselected attacks occurring in forty-four patients seen between June, 1943, and October, 1945. Eight of the fifty patients died, an immediate mortality rate of 16 per cent. It was noteworthy that all of the twenty-six patients who were treated for their first attack survived. In only one case was there clinical evidence of a pulmonary embolus and this patient had been given an inadequate dose of dicumarol. In six autopsied cases no mural thrombi, systemic or pulmonary embolic phenomena were found. In a recent personal communication, Nichol has informed the author of a patient who, having suffered three serious attacks of coronary thrombosis with myocardial infarction, has been on dicumarol therapy for more than forty months with no further attacks of coronary thrombosis and with no toxic effects of dicumarol. He did have one episode of severe bleeding from a peptic ulcer. In February, 1946, Peters, Guyther and Brambel[56] reported their experiences using dicumarol in acute coronary thrombosis, beginning in March, 1943. They compared fifty dicumarolized patients with sixty nondicumarolized patients, and reported the following results: In the group of sixty patients who did not receive dicumarol, there were seventeen with congestive failure who were given digitalis. Of these seventeen, nine or 53 per cent died, most of them as a result of embolism. In the group of patients receiving dicumarol, eight were given digitalis for congestive failure. One of these (12.5 per cent) died, apparently of renal complications. In the sixty patients receiving conventional treatment for coronary thrombosis, the incidence of clinical embolism was 16 per cent and the mortality rate was 20 per cent. By contrast, in the fifty patients receiving the conventional treatment plus dicumarol sufficient to maintain their plasma prothrombin activity at 35 to 50 per cent of normal, the incidence of clinical embolism was 2 per cent and the mortality rate was 4 per cent. They reported an increased clotting tendency as evidenced by a decrease in the prothrombin clotting time (12.5 per cent diluted plasma) in most of their patients with acute coronary thrombosis. They also concluded on the basis of figures mentioned above that digitalization for congestive failure in coronary thrombosis increases the incidence of thromboembolic phenomena and that this hazard may be nullified by dicumarolization of such patients. Parker and Barker[57] have recently reported fifty additional cases of myocardial infarction and have compared the results with 100 cases treated conventionally in the series of Nay and Barnes. They were as follows: deaths in the controls, 13 per cent—anticoagulant cases, 10 per cent; thromboembolic complications in the controls, 37 per cent—anticoagulant cases, 4 per cent. In addition to the above four groups of workers, a few individuals have reported isolated cases and small series of patients treated with dicumarol therapy.

All of the material presented thus far is open to the following criticisms:

1. The various series reported are too small to be statistically conculsive.

2. In no series have alternate cases been studied so that the selection of cases not treated with dicumarol may not be completely unbiased and they cannot therefore be accepted as absolutely valid controls.

PRESENT AND FUTURE STUDIES REGARDING THE USE OF ANTICOAGULANTS IN THE TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

The American Heart Association has therefore established a Committee for the Evaluation of Anticoagulant Therapy in the Treatment of Coronary Thrombosis with Myocardial Infarction. The work of this committee has been subsidized by a grant from the U. S. Public Health Service. The work is being carried on actively in fifteen hospitals at present. All patients suffering from coronary thrombosis with myocardial infarction admitted on the participating services of these hospitals on odd days of the month receive anticoagulant therapy. Patients admitted on even days of the month do not receive it. Careful records are being compiled on master forms which are being forwarded to the central office of this study at The New York Hospital, where they are being subjected to statistical study and analysis. It is anticipated that from 800 to 1,000 cases will be studied. The results should be sufficiently large and statistically valid. The figures at present are encouraging, but it is too early to consider them as definitive or not subject to marked change with larger numbers. In some of these hospitals patients receive heparin during the first two days of treatment while the action of dicumarol is becoming effective. Further studies regarding the desirability of giving heparin immediately in all cases are being planned. Particular attention to this phase of the study is being paid by Glueck and her co-workers[58] at Cincinnati, and the results to date have been favorable.

In an unpublished survey of 111 cases of myocardial infarction studied from 1932 to 1936 under the supervision of the Laboratories of Pathology, Bellevue Hospital and New York University College of Medicine, Graef[59] noted that myocardial lesions bore an inconstant relation to the state of coronary arteries. In ten cases (9 per cent) there was no gross or microscopic evidence of coronary occlusion, thrombotic or atherosclerotic occlusion. The great majority (91 per cent) had multiple occlusions of different sorts in one or both coronary arteries. Of the 101 cases with occlusion, sixty-three had thrombotic occlusion (always in the presence of arteriosclerosis) while the rest had atherosclerotic narrowings of various degrees. However, it was noted that in those with thrombotic lesions the thrombi were quite variable in estimated age when compared with the co-existing infarcts. In thirty cases with recent fresh infarction seventeen had fresh unorganized thrombi in coronary vessels supplying the affected area, while two had old organized thrombi. In the remaining eleven cases there were no thrombotic lesions; these had marked narrowing in one or more places in the coronary arterial tree. In fifty-three subjects with old myocardial infarcts twenty-five had old coronary thrombi while six had fresh thrombi.

It seems possible, therefore, that thrombosis may follow infarction due to coronary insufficiency, the myocardial fiber swelling and necrosis impeding capillary flow, leading to stasis in the nutrient artery or arterioles. Where arteriosclerosis pre-existed and produced narrowing, such stasis might then lead to local thrombosis.

These data suggest that in certain individuals who have lived through a prelimi-

nary myocardial infarction, there may be subsequent thrombosis with an increased area of infarction producing serious later effects or perhaps even death.

It is highly probable on the basis of many observations that most thrombi, however small, having once occurred, do tend to propagate during the early hours or even days of their existence. This may be minimized by immediate heparinization, following which dicumarol may be continued over a longer period of time. This problem will be studied further by the committee. Another investigation which should be undertaken is the follow-up observation of patients who have received anticoagulant therapy and have thus survived one attack. Their outlook for the future should be evaluated. A follow-up study should also be undertaken of individuals who can continue dicumarol therapy over a long period of time in order to determine whether their prognosis is thereby improved, as compared with individuals who are not able to continue long-term dicumarol therapy. These represent a few of the problems to be considered in the future.

USE OF ANTICOAGULANT THERAPY IN THE TREATMENT OF THE THROMBOEMBOLIC COMPLICATIONS OCCURRING WITH RHEUMATIC HEART DISEASE AND AURICULAR FIBRILLATION

Another challenging group of patients in whom intracardiac thrombosis is a very important problem are those who have suffered from rheumatic fever and years later develop auricular fibrillation and intracardiac thrombi. These thrombi then propagate and release emboli from time to time. Such a series is now under our observation.[44,60] The study of this group of patients seemed worth while after observing the results of the use of anticoagulants in patients who had developed multiple emboli associated with auricular fibrillation secondary to coronary thrombosis. We were further stimulated by Dr. Harvey Ewing, who referred the first patient for this specific purpose. Thirteen such patients have been treated and eleven are being followed at this time with continuous ambulatory treatment; one has died; another has taken the treatment too irregularly to allow any conclusions.

The following histories are given as examples of this type of patient and of the problems involved in their treatment.

E. S., a female, forty-seven years of age, had typhoid fever at three years of age, scarlet fever at four years and rheumatic fever at five years. Rheumatic heart disease was recognized during the sixth year. Chorea was diagnosed at six, ten and twelve years. Since the age of thirty-three her heart had been in a constant state of auricular fibrillation, and during these years she had taken digitalis almost constantly. In 1935, she had an embolus to the left groin and also a pulmonary embolus. In 1942, she had a left cerebral embolus which produced a right hemiplegia from which she made a complete recovery. During the years of 1943 to 1944, it was estimated that she had at least six emboli, which were apparently small, in various locations throughout her body. In December, 1945, she developed two emboli, one renal and one mesenteric. In January, 1946, she developed her thirteenth definite embolus which was pulmonary, and in September, 1946, her fourteenth embolus which was also pulmonary. On November 15, 1946, she became decompensated. Two days later, she developed a fifteenth embolus to the right arm. This produced coldness, blanching, loss of pulsation below the elbow and appeared to endanger the arm. On November 19th, she developed the sixteenth embolus which was to the left leg; on November 25th, a seventeenth to the right lung field; and on December 3rd, her eighteenth to the right lower quadrant of the abdomen, which produced shock, paralytic ileus and later blood in the stool. On December 3rd, she developed her nineteenth embolus, which was to the left leg, and on December 6th, her twentieth which

was to the left forearm and produced marked generalized shock. The patient was acutely ill. Her outlook appeared extremely serious.

On the day of her twentieth embolus, because of her desperate condition, she was started on anticoagulant therapy despite the blood in her stools, which was believed to be secondary to a mesenteric infarction. She received 52.5 mg. of heparin intravenously at 9:00 P.M., December 6th; 52.5 mg. at 1:00 A.M., December 7th, and 50 mg. at 6:15, December 7th. She was also given 300 mg. of dicumarol on December 6th, followed by daily doses of 200 mg., and thereafter was regulated in accordance with the schedule previously outlined in this paper. She was continued for one month on this regimen while in the hospital. Her average requirement of dicumarol was 100 mg. five times weekly.

She was discharged from the hospital on January 6th, having immediate cessation of her embolic phenomena and a completely uneventful course following the administration of anticoagulants. She has since continued to receive anticoagulant therapy while ambulatory. She has had several episodes of ecchymoses of mild degree. Her prothrombin time has in general been kept between 25 and 35 seconds, the highest having been 44 seconds. At present her average dose is approximately 50 mg. of dicumarol per day. No further embolic episodes have occurred. The patient's general condition is excellent. She is able to travel and does so freely and without difficulty whenever satisfactory prothrombin studies can be arranged. Her heart continues to be in a state of compensated auricular fibrillation.

M. T., a female, thirty years of age, had had scarlet fever at the age of thirteen. No diagnosis of frank rheumatic fever was ever made. In 1940, she began to develop episodes of rapid heart action with paroxysms of orthopnea. In 1946, she had her first recognized embolus. This was a cerebral embolism to the left side producing aphasia and numbness of the right arm and unconsciousness. She made a complete recovery from this. On December 29, 1946, she had an embolus to the right leg. On January 2, 1947, she developed auricular fibrillation and heart failure. She was then hospitalized. On January 7, 1947, she developed what was apparently a splenic infarct; on January 9th, another left cerebral embolus; on January 10th, dicumarol was begun; and on January 11th she had a probable mesenteric embolus. On January 17th, she developed mild abdominal pain which might conceivably have been an embolus; this was not definite. The prothrombin time at that time was 32.7 seconds. On February 7th, she was discharged from the hospital for ambulatory treatment. Her average requirement is 400 mg. of dicumarol weekly. There have been no further emboli.

C. C., a female, forty-seven years of age, developed rheumatic fever with decompensation in 1932. In 1933, she had a second attack of rheumatic fever. In 1938, she had a period of decompensation. In 1941, she again developed decompensation with the first recognized auricular fibrillation and flutter. In October, 1941, she presented her first embolic episodes. Her first embolus was to the right brachial artery. She then developed either a saddle embolus or emboli to both femoral arteries. In January, 1942, a right middle cerebral embolus occurred. In April, 1942, emboli involved both kidneys, the right brachial artery, both femoral arteries, probably an artery in the base of the spine and definitely the right third finger. In September, 1942, she became decompensated again. In March, 1944, she had another episode of emboli to both kidneys. In April, 1945, she developed a myocardial infarction. In January, 1946, a fairly definite saddle embolus occurred from which she recovered remarkably. In March, 1946, she again became decompensated and this recurred in September, 1946. On September 23rd, she had a shower of emboli to the cerebrum and to the mesenteric and peripheral vessels. On October 5, 1946, she developed a pulmonary embolus with infarction.

On October 11, 1946, dicumarol was started. At that time she had a questionable thrombophlebitis which had largely but not completely subsided. It finally did subside. On November 20, 1946, she had pinkish sputum but no pain. There was considerable doubt whether this was due to a pulmonary embolus or not. The prothrombin time then was 24.1 seconds, which is below a definite therapeutic level. On November 26th, she was discharged from the hospital

having had dicumarol for forty-seven days during which time she had one questionable embolus. From that time until January 22nd she remained at home where she received no dicumarol and was in a state of persistent decompensation and fibrillation.

On January 22, 1947, she was readmitted to The New York Hospital with pulmonary and mesenteric emboli. On January 23rd, she had additional pulmonary and probably a splenic embolus. Dicumarol was again started. On January 25th, she had boring pain in the back opposite the left eleventh rib. There was no hemoptysis. There was some question as to whether this was an embolus or not. On February 7th, she was discharged from the hospital having had dicumarol for fifteen days. No further emboli occurred during that time. The patient returned to her home. No satisfactory arrangements could be made for continued anticoagulant therapy.

The patient remained in bed at home, receiving digitalis 0.1 Gm. daily, ammonium chloride 2.0 Gm., three times a day, and mercupurin injections twice weekly. There was persistent pain in the abdomen and right leg, also dyspnea and frequent attacks of vomiting, but no bleeding or hemoptysis. On March 17, 1947, she suffered severe pain down the right leg and severe occipital headache, and on the following day there was sharp pain in the left anterior chest with severe cough productive of rusty sputum and chills.

The patient was readmitted to The New York Hospital, her twelfth admission, on March 19, 1947. Physical examination upon entry revealed a temperature of 40.3°C., dyspnea and cyanosis, dullness to percussion at the right base and many râles upon auscultation of the left lower axilla and base posteriorly. The cardiac rhythm was grossly irregular, beats were frequently coupled and there were occasional runs of rapid, regular rhythm. There was a systolic murmur in the tricuspid area and both systolic and diastolic murmurs over the aortic and mitral areas. A pulsating liver could be felt 7 cm. below the costal margin. There was a 1 plus ankle edema. Diagnoses upon entry were: (1) Rheumatic heart disease with enlarged heart, auricular fibrillation, mitral and aortic stenosis, mitral and aortic insufficiency, tricuspid insufficiency, decompensated; (2) chronic passive congestion of the lungs and liver and hepatomegaly, possibly secondary to cardiac cirrhosis; (3) possible bacterial pneumonia; and (4) possible pulmonary infarct of recent origin.

The patient was treated with penicillin, 300,000 units twice a day for five days and 300,000 units daily for five days with defervescence and general improvement. Dicumarol was started on March 21, 1947, and the patient received 1,000 mg. in six days reaching a prothrombin level of 43.5 seconds on the eighth day. On March 27, 1947, the patient coughed up clots of blood and suffered very mild low substernal pain. Prothrombin time was 39.7 seconds and dicumarol was discontinued. On the next day the patient coughed up 100 cc. of fresh blood. Her prothrombin time was 43.5 seconds. Hykinone, 72 mg., was given intravenously and the hemoptyses subsequently decreased in amount. On April 1, 1947, the patient was still coughing up blood and, although no dicumarol had been given, the prothrombin time was 36.1 seconds. Vitamin K was given intravenously in a dose of 72 mg. On April 2nd, there was a hemoptysis of 300 cc. of blood, and the prothrombin time was 29.7 seconds; 72 mg. of vitamin K was injected intravenously and a blood transfusion of 500 cc. of whole blood was given. On the following day hemoptysis had decreased to about 50 cc. and the prothrombin time had fallen to 23.0 seconds. Respirations were rapid, 34 per minute, and râles were heard in all lung fields. On April 4, 1947, there was an episode of sudden and severe dyspnea. Breath sounds were diminished over the left chest. The pulse was 130 beats per minute and respirations were 36 per minute. A portable x-ray of the chest revealed hilar infiltration in the left lung with markings accentuated to the periphery. The prothrombin time was 19.0 seconds and there was no hemoptysis. The patient became progressively dyspneic and cyanotic and expired April 5, 1947.

Autopsy revealed the following pathological findings: There was advanced chronic rheumatic heart disease with stenosis and insufficiency of the mitral, aortic and tricuspid valves. The heart weighed 600 Gm. and was moderately

dilated and hypertrophied. There was thickening and fusion of the leaflets of the tricuspid valve (7.5 cm. circumference) and of the mitral valve (5.0 cm. circumference) with fusion, thickening and shortening of the chordae. The aortic cusps were thickened and the commissures were fused (circumference 6.5 cm). Beneath the aortic valve there was a pocket-like thickening of the endocardium. There was an old organized mural thrombus in the left atrium. There was an old infarct involving the apex and septum of the left ventricle and old infarcts of the spleen and kidneys. Despite the extensive scarring and thinning of the apex of the left ventricle and of the septum with aneurysmal bulging and fibrous pericardial adhesions over the area, no occluded vessel to the region was found.

There was advanced confluent lobular pneumonia with advanced chronic passive congestion, edema and partial collapse of the lungs, which weighed 1,570 Gm. There were firm, red, consolidated areas in the lower lobes and scattered similar areas elsewhere. A cast of clotted blood was found to occlude the left main bronchus and its major branches and there was a moderate amount of bloody mucoid material in the bronchi to both lungs. There was advanced chronic passive congestion, fatty degeneration and moderate cardiac cirrhosis of the liver, which weighed 1,600 Gm. and was moderately and finely nodular.

The possibility of influencing the prognosis of this patient favorably was believed from the beginning to be especially poor because no anticoagulant therapy could be arranged at home, and because the living conditions of this patient were never satisfactory for good care. The part dicumarol played in the production of the terminal hemorrhages is open to question but it must be seriously considered. This case is included to illustrate the difficulties which may prevent the use of anticoagulant therapy in the home care of some patients.

L. B., a female, thirty-eight years of age, developed rheumatic fever at four years of age. From then until she was twelve she had multiple attacks of rheumatic fever with the development of a heart lesion. In 1941, she developed auricular fibrillation, was found to have mitral stenosis with cardiac decompensation. In February, 1946, she had a severe saddle embolus. She was then given heparin for two weeks. The embolus apparently divided, descending into both legs, and leaving her with occlusion of the major arteries above the knees bilaterally. In 1946, between February and June, she suffered six embolic episodes again involving her legs and also her abdomen and brain. In September, 1946, she had another embolus to her right foot, and again one to both legs. On November 2, 1946, she developed a cerebral embolus which produced dizziness, diplopia, slurring of speech, involuntary twitching of the right arm, occipital headaches and loss of convergence of the left eye. She was admitted to The New York Hospital on November 3rd and dicumarol was started at that time. She remained in the hospital for one month, since which time she has been ambulatory. Her average weekly requirement of dicumarol is somewhat higher than that of most patients. She needs approximately 900 mg. per week to maintain a level between 28 and 35 seconds. She has had no further emboli and leads a rather active life.

B. C., a female, fifty-three years of age, developed rheumatic fever at twenty-eight years of age, and had five recurrences thereafter. She developed auricular fibrillation approximately five years before admission. It has been paroxysmal, with great variations in the duration of attacks. Her first recognized embolus occurred in 1944. This was cerebral and she became unconscious and was in bed for approximately six weeks. She made a complete recovery. The second embolus occurred on May 30, 1946, producing a sudden blackout. This was also probably cerebral. In June, 1946, she had emboli to both legs. On July 7, 1946, she developed a sharp pain in the right hip and also one in the chest followed by bloody sputum which was probably a pulmonary embolus. On July 14, 1946, she developed one to the right leg. Anticoagulant therapy was not started at that time but was begun on September 24, 1946. She received dicumarol while in the hospital for one month, since which time she has been ambulatory. She requires approximately 400 to 500 mg. of dicumarol per week. On December 16th, she began to have excessive menstrual

flow which continued for approximately 10 days. Her prothrombin time ranged between 24 and 28 seconds so it seems unlikely that this was responsible for her excessive flow. The dicumarol was discontinued and vitamin K, two doses of 64 mg. each, was given. A gynecologist believed that the excessive flow was due to menopausal changes and a dilatation and curettage was performed, followed by irradiation. She began her dicumarol again, thereafter, and there have been no emboli following dicumarol.

Other examples could be cited to illustrate this type of case and the problems which may be encountered.* It should be pointed out that these patients characteristically may go for many months or even for several years without embolic episodes. Therefore, caution should be used in evaluating the effects of therapy in any specific case. On the other hand, one should note that several of these patients were in serious condition and were having very frequent and alarming embolic episodes at the time anticoagulant therapy was begun. Eleven of the thirteen patients who are receiving ambulatory dicumarol treatment, and who have been able to follow this therapy with satisfactory prothrombin tests, have now gone for a total of seventy-five months (or more than six years total time), without an embolus. Two patients who have been unable to remain on satisfactory ambulatory anticoagulant regimens have had embolic phenomena following a course of dicumarol for one month or more in the hospital. One of these, as above reported, died. The results, while at present inconclusive, appear sufficiently encouraging to warrant further study and consideration of anticoagulant therapy in the care of this most unfortunate syndrome, hitherto practically unamenable to treatment.

* The first preliminary report was presented before the Philadelphia College of Physicians in November, 1946.

USE OF ANTICOAGULANTS IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

The use of heparin in the treatment of subacute bacterial endocarditis has been controversial. Katz and his co-workers[51] attempted to modify the course of this disease with heparin. Kelson and White[52] also reported on its use in connection with sulfonamides but the treatment of this disease with sulfonamides, with or without heparin, was abandoned because successes were rare; and the recovery rate deviated little from that resulting from spontaneous remission independent of the use of either chemotherapeutic or anticoagulant agents. MacNeal, Marty and Poindexter,[61] Dawson et al.,[62] and Loewe and his co-workers[63–66] were among the first to use penicillin therapy successfully in the treatment of bacterial endocarditis. Loewe et al. combined this with heparin therapy on the basis of observations that fibrin and blood elements served as an impenetrable barrier to effective chemotherapeusis. The offending organisms lying deep in the vegetation were well protected from circulating anti-infective agents. They believed that to accomplish disappearance of vegetations the combined use of a suitable chemotherapeutic agent and an anticoagulant was required. In Loewe's laboratory heparin was employed in experimental animals to arrest the deposition of blood platelets and fibrin which served as a protective nidus and as a stimulus for bacterial growth. They reported that relatively fresh, artificially induced thrombi in the animal could be dissipated following the use of anticoagulants. They also made observations on human postmortem material which they believed indicated that heparin had a possible erosive effect on endocardial vegetations. This experience was applied to human patients, using the continuous intravenous infusion of heparin and the fractional intravenous in-

jection method. Since these methods had marked technical and clinical disadvantages, Loewe utilized a retarding base—the Pitkin menstruum—composed of gelatin, dextrose, glacial acetic acid and water. Although a prolonged anticoagulation effect was obtained, the use of the original preparations was complicated by local pain, occasional severe local reactions and nausea in some individuals. Loewe and his group, in collaboration with others, have been striving to obtain or perfect a more satisfactory menstruum. As above mentioned, they claim to have reduced these adverse effects while maintaining therapeutic effectiveness.* Our patients still complain of pain after injections of the newer preparations. Using combined penicillin-heparin therapy Loewe et al. have reported a recovery rate of 83 per cent in 115 consecutive and unselected patients with subacute bacterial endocarditis. This is a remarkable recovery rate in a disease formerly considered practically incurable. The question has been repeatedly raised as to whether heparin *per se* actually plays a part in this recovery rate. Other workers[6,7] have reported recovery rates from penicillin alone ranging from 60 per cent to higher than 80 per cent. There has been a considerable difference in the amount of penicillin which the various groups have utilized in the treatment of their patients and Loewe has employed the largest doses recorded. As far as the present author knows, there has been no definite correlation made as yet between the dosage used and the actual statistics reported in the various series. This would be useful. It might shed some light on the importance, or lack of importance, of heparin as a therapeutic agent. It was noted early in the use of penicillin that thrombophlebitis was a rather troublesome complication and Loewe pointed out that thrombophlebitis seldom occurs in his heparinized patients, which would be one point in favor of using it. On the other hand, hemorrhagic manifestations and even death have occurred from the use of both heparin and dicumarol in the treatment of subacute bacterial endocarditis. The cause for these hemorrhagic manifestations in various areas of the body in cases of subacute bacterial endocarditis is not clear. One possibility appears to be that the effect of the disease is more widespread throughout the endothelial system than has hitherto been recognized. The work of Moldavsky, Hasselbrock and Cateno,[5] and of Macht[6] demonstrating the marked increase in the tendency toward thrombosis produced by the administration of penicillin should reopen this subject. Macht[7] found that amorphous penicillin of every brand examined produced a marked acceleration of clotting time, whether injected intravenously or intramuscularly, or even when administered by a stomach tube mixed with aluminum hydroxide gel. The crystalline salts of the various types of penicillin were studied. They were found to affect the thromboplastic properties in the following order: The most potent was penicillin X (hydroxybenzyl penicillin), next came K (heptyl penicillin), G (benzyl penicillin) and F (pentyl penicillin). It was found, furthermore, that a small dose of penicillin X added to penicillin G produced a synergistic effect and hastened coagulation more than a dose of penicillin G alone. Since much larger doses of penicillin are now being administered in some cases of subacute bacterial endocarditis, the question of the use of anticoagulants to counteract the coagulant effect of massive doses of penicillin should be studied further. It is obviously undesirable to produce an increase in the thrombosing tendency when the patient is bedridden and a vegetation is forming within the heart. On the other hand, it is equally important to avoid facilitating hemorrhage.

* Personal communication from Dr. Leo Loewe.

At the present writing we must conclude that the evidence that anticoagulants favorably affect the results of penicillin therapy in subacute bacterial endocarditis is inconclusive. There is evidence that their use may increase the risk of hemorrhage. On the other hand, further study to determine their power to control the thrombosing tendency of the large doses of penicillin now used is justified at this time.

SUMMARY AND CONCLUSIONS

Thromboembolic phenomena occurring in all parts of the vascular tree, particularly in the heart, lungs, brain and peripheral vessels, produce the terminal episode in the lives of more persons over fifty than any other cause. A large proportion of these patients survive their first episode of thrombosis or embolism but die later of recurrences or of complications.

Treatment of heart disease in the past, while helpful, has in many ways tended to encourage further thrombosis, the very complication frequently most important to avert. The use of the anticoagulants heparin and dicumarol constitutes a logical procedure to combat this tendency to thrombosis.

The results of anticoagulant therapy in the treatment of thrombophlebitis of the peripheral veins, together with the secondary complications of this syndrome, are summarized. These reports are drawn from the experiences of the Mayo Clinic, the Swedish hospitals, and our own experiences in both military and civilian hospitals. They appear to demonstrate conclusively that this form of therapy is the most satisfactory used to date.

The evidence in favor of the value of anticoagulant therapy in the treatment of coronary thrombosis with myocardial infarction, especially in the presence of thromboembolic complications, appears definitely encouraging. Case reports are presented exemplifying this problem. Final evaluation must await the results of large, carefully controlled studies such as that now being carried on in fifteen participating hospitals under the auspices of the American Heart Association and the U. S. Public Health Service.

The value of anticoagulant therapy in the treatment of rheumatic heart disease with auricular fibrillation and multiple emboli is under investigation. Detailed case reports of some of the first patients studied in this series are presented. The results warrant further study of this problem.

The evidence for the specific value of the addition of anticoagulant therapy to penicillin in the treatment of subacute bacterial endocarditis is inconclusive at this time. The increased tendency to thrombosis produced by massive doses of penicillin injects a factor which may reopen this subject for further study.

The efforts summarized in this paper represent a fresh point of view toward and a new method of attack upon some of the most difficult and heretofore insoluble problems of heart disease. The results, while at present preliminary, have been encouraging beyond expectations and justify more intensive exploration by this approach.

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Present Status of the Problem of Thromboembolism*

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DURING the past six months the Seminars on Thromboembolism have reviewed the concepts of this disease and have presented the results of the various schools of therapy. The increasing importance of the problem and the interest of the medical profession in attacking it has been reflected in the high caliber of the work reported from so many widely separated medical centers.

COAGULATION MECHANISMS

Ferguson,[1] in reviewing the basic mechanisms of coagulation, indicated the possible ways in which pathologic intravascular clotting may occur. It is the belief of many investigators that an as yet unidentified precipitating factor produces a state of accelerated coagulability of the blood which may then reveal itself clinically in one or more thrombotic phenomena. Present methods of estimating the state and speed of coagulation are admittedly gross and insensitive. However, a number of investigators have reported observations indicating alteration of blood coagulability under varying clinical conditions. (Table 1.) These changes may in themselves predispose to abnormal clotting or they may indicate periods of actual hypercoagulability.

The most pressing need today in the thromboembolic problem is for a simple test for blood coagulation which is easily and quickly performed. By means of this test the individual with a propensity to pathologic intravascular clotting could be discovered in the prethrombotic period and aggressively and intelligently treated with appropriate prophylactic measures, either medical or surgical.

During the past several years interest has been stirred by observations that certain drugs appear to exert a coagulation-accelerating or thromboplastic-like action. Digitalis was the first to be so incriminated. The original report[19] was followed by studies by three other groups of investigators who noted that following and during digitalization the coagulation time,[20–22] the heparin tolerance[21] and the dilute prothrombin time[6] were reduced. Loewe[16] goes so far as to say that because of this thromboplastic-like side effect digitalis should be avoided if possible during the period of heparinization. On the other hand, three reports[23–24a] have been published showing completely negative findings with regard to acceleration of coagulation by digitalis preparations. Thus, the problem is not conclusively settled as to just what is the rôle of this side action of digitalis and of precisely what magnitude. It would seem logical to administer digitalis whenever it is indicated, particularly in congestive heart failure associated with cardiac infarction and the severe types of pulmonary embolism. Moreover, if anticoagulants are being employed in the management of a patient with a thrombotic problem, either heparin or dicumarol would theoretically be able to nullify any coagulant effect of the digitalis.

Equal interest has been aroused by preliminary reports[25,26] that penicillin also appears to produce acceleration of coagulation. However, one investigator[27] has failed to demonstrate the presence of any thrombo-

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plastic-like activity exerted by penicillin in *in vitro* and *in vivo* tests. Some of the more highly purified commercially available penicillin preparations and the penicillin G fraction exhibit much less of this clot-accelerating activity. As with digitalis, this alleged liability of penicillin is not considered at present to be a contraindication to its use either in thromboembolic cases or in infections. After more experimental and clinical evaluation the actual rôle played by penicillin as a possible inciting agent in intravascular clotting may be more judiciously weighed. The evidence now is far from sufficient to warrant administering anticoagulants prophylactically when penicillin is given or to withhold penicillin, because of its possible thrombotic threat, from a patient in whom it is indicated.

Wright[28] has summarized the present status of aminophylline as a coagulant. The evidence to date fails to establish any coagulation-accelerating or hyperprothrombinemic activity of this drug.

TABLE I

OBSERVATIONS INDICATING TENDENCY TO INCREASED COAGULABILITY OF THE BLOOD IN CERTAIN CLINICAL STATES

Test	Trend of Results	Clinical State Encountered	Investigator
Platelet count	Increased	Postoperative; post partum	Wright[2]
Platelet count	Increased	Postoperative	Shapiro[4]
Platelet adhesiveness	Increased	Postoperative; post partum	Wright[2]
Blood coagulation time	Accelerated	Postoperative; post partum	Dawburn[3]
12.5% dilute prothrombin time	Decreased	Thrombosis or pulmonary embolism	Shapiro[4,5]
Whole or dilute prothrombin time	Decreased	Acute coronary thrombosis	Peters et al.[6]
Plasma clotting index	Increased	Thromboembolism	Bancroft[7]
Intravenous heparin tolerance	Increased	Acute thrombosis	de Takats[8]
Heparin retarded clotting time	Flattened curve	Bed rest; acute inflammations; postoperative	Waugh[9]
Modified heparin retarded clotting time	Decreased	Acute coronary thrombosis	Ogura[10]
Dilute prothrombin time	Decreased	Acute coronary thrombosis	Meyers[11]
Venous clotting time	Decreased	Venous blood from acute thrombophlebitic extremities	Shafiroff[12]
Dilute prothrombin time	Decreased	Venous thrombosis; pulmonary embolism	Cotlove[13]
Whole and dilute prothrombin time	Decreased	Post partum	Norris[14]
Venous clotting time in lucite tubes	Decreased	Thrombophlebitis	Kadish[15]
Platelet clustering	Increased	Thromboembolism	Loewe[16]
Heparin dose necessary to produce usual prolongation of venous clotting time	Increased	Acute thrombosis	Loewe[16]
Blood coagulation time	Decreased	Postoperative; post partum	Dawburn[3]
Clot retraction time	Accelerated	Pulmonary embolism	Hirschboeck[17]
Blood "fibrin"	Increased	Postoperative	Walters[18]

EARLY AMBULATION

Early or accelerated ambulation of the post partum and postoperative patient, and even of medical and cardiac patients, has been considered to be a logical approach in attempting to reduce the incidence and mortality of thromboembolism. It was believed that venous stasis and the sluggish circulation of a person in bed would be altered advantageously by earlier mobilization, thus eliminating a factor considered to be of major importance in the production of thrombosis. Some reports of series managed by early ambulation have indicated a significant reduction in incidence and mortality both as regards peripheral thromboses and pulmonary embolism. Jorpes[29] accumulated statistics on early ambulation from the European clinics in which the occurrence of thrombosis was reduced up to one-half of the original figure. At the same time, he concluded that such measures do not provide full security against the occurrence of this complication. Canavarro[30] reported a re-

duction in incidence of thrombotic phenomena of over 50 per cent (from 2.4 to 1.0 per cent) in a series of 500 surgical patients ambulated in the early postoperative period. Leithauser,[31] an enthusiastic advocate of accelerated ambulation, reported a series of over 2,000 patients under his observation in which no pulmonary emboli and only two instances of thrombophlebitis occurred.

On the other hand, Blodgett[32] studied 238 cases of early postoperative ambulation at the Massachusetts General Hospital and failed to find any decrease in thrombotic complications, even noting a statistical increase in the incidence of phlebitis, pulmonary infarct and deaths due to pulmonary emboli. During the past two years it has appeared to the author that there are definitely more cases of thromboembolism occurring currently than ever before, whether due only to the increased alertness in diagnosis or also to an absolute increase in the occurrence of this disease is not clear. This impression prevails despite the emphasis currently placed upon the avoidance of unnecessary bed rest and the general adoption of programs of early ambulation. Powers[33] has analyzed his experience in a large group of patients under his direct supervision and failed to demonstrate any reduction in the occurrence of thromboembolic phenomena. The fatalities from pulmonary emboli were decreased by 50 per cent. However, Powers rightly points out that recently adopted definitive treatment (by vein ligation in his clinic) must claim at least part, possibly the major part, of the credit for the reduced mortality rate. At any rate, it is now even more apparent that although accelerated ambulation is physiologically sound and a step in the right direction, it is far from the panacea or complete prophylaxis of thrombosis that had been hoped not so long ago. Other and more specific prophylactic measures are worth while and necessary. Even more, a high index of suspicion of thrombosis must always be present in the clinician's mind in order to diagnose the process and institute specific treatment as early as possible. He should not be lulled into a false sense of security because he sees to it that his patient is out of bed as soon as possible. The physician's obligation in avoiding thrombotic complications has not been met merely by ordering early ambulation.

VENOUS THROMBOEMBOLIC DISEASE

Prophylaxis. Inasmuch as avoidance of unnecessarily prolonged bed rest by accelerated ambulation has not eliminated thrombotic phenomena, it is only logical to attempt to single out those individuals who are in situations which clinical experience has shown to predispose to thromboembolism (e.g., postoperative, cardiac infarcts, etc.). Active specific prophylactic measures could then be carried out, either by the use of anticoagulants or by peripheral venous ligation.

Extensive clinical observations and critical analyses of many series of patients indicate that the following facts are pertinent to the detection of thrombosis-susceptible patients:

1. A history of previous thromboembolism predisposes to recurrence, particularly if that individual again becomes postoperative or post partum.
2. Disturbances of venous circulation, such as extensive varicosities, favor the development of thromboses.
3. Individuals with malignancy suffer more frequent and recurrent thromboses.
4. Extensive abdominal and pelvic surgical procedures, particularly those performed for malignancy (such as abdominoperineal resection for cancer of the rectosigmoid), are complicated by far more than the average number of thrombotic phenomena (about 35 per cent in our experience).
5. Fractures of the femur and amputations of lower extremities are followed by a remarkably high incidence of thromboembolism (as high as 10 per cent of fatal embolism in older patients).

6. More than 60 per cent of all postoperative venous thromboses and emboli occur in the age group over fifty years and more than 80 per cent in the age group over forty years.
7. Thromboembolism occurs at least twice as frequently in obese individuals as in those of normal weight.
8. Cardiac insufficiency, with its attendant disturbances of venous return, greatly increases the risk of thrombotic episodes.

Indications for prophylactic therapy, such as the aforementioned factors, are still being drafted and put to therapeutic test. Recent reports, particularly from the Mayo Clinic,[34] Allen and his group at the Massachusetts General Hospital,[35] Murray in Canada[36] and Crafoord in Sweden,[37] indicate a significant decrease in the incidence of and deaths due to thromboembolism following institution of active specific prophylactic measures (i.e., anticoagulants or vein ligation). The results obtained in the field of prophylaxis by both medical and surgical management are comparable and encouraging.

Diagnosis. The clinical diagnosis of venous thrombosis and pulmonary embolism was discussed by the Columbia and Cornell Conferences,[38,39] by Loewe[16] and was also well outlined by Homans in a previous publication.[40] Essential to the proper care of patients with thrombotic problems is an understanding of the mechanism of the development of deep venous thrombosis, particularly in the lower extremities.[38] The clinician should possess a mental picture of the two clinical extremes of venous thrombosis (phlebothrombosis and thrombophlebitis) and the manner in which a pulmonary embolus evolves from peripheral deep thromboses; he should also be alert for the earliest evidence of the presence of thromboembolic disease. Homans[41] has differentiated instructively the two phases of pulmonary embolism, i.e., the embolic phase and the phase of infarct production. Patients in these phases differ symptomatically and present varying physical findings. X-ray evidence may be absent in the purely embolic phase. It is not amiss to re-emphasize that the occurrence of pleuritic pain in a postoperative, post partum or cardiac patient or the occurrence of hemoptysis, particularly in a cardiac patient, should immediately suggest the possibility of embolism. Under such circumstances the slightest clinical indication of deep venous thrombosis should be weighty evidence confirming the impression that pulmonary embolization has occurred. Bearing in mind that as many as 50 per cent of pulmonary emboli occur without clinically recognizable peripheral venous thrombosis at the time of embolism,[39,42] the absence of clinical evidence of peripheral venous thrombosis should bear no weight whatsoever against a diagnosis of pulmonary embolism. If venous thrombosis is present, the diagnosis can be made that much more easily.

Rationale of Therapy. The major objectives of therapy in deep venous thrombosis and/or pulmonary embolism are: (1) The proper management of the original episode of acute pulmonary embolism so as to reduce, insofar as possible, the associated mortality rate; (2) the prevention of subsequent massive pulmonary emboli which may be fatal; (3) the proper handling of the thrombotic occlusion of the deep venous system so as to retain as near normal the state of venous competency in the post-thrombotic years and thus to avoid the troublesome "postphlebitic syndrome."

The advocates of surgery argue that complete interruption of the pathway which 90 per cent of emboli are believed to traverse is not accomplished by medical methods. Ligation is said to offer the patient a complete and permanent type of protection without the added risk of hemorrhage. The anticoagulant group agree that this contention, particularly in reference to bleeding, may well be borne out in certain situations (e. g., neurosurgical and prostatic surgery). On the other hand, the medical proponents believe that the thrombotic process or embolus is merely a local manifestation of a generalized thrombosing tendency. They

argue that if prophylaxis against subsequent fatal emboli can be obtained without the discomfort or risk of an additional operation, this is desirable. The medical approach is believed to be more physiologic and equally effective as borne out by clinical reports. Bleeding of significant degree occurs in not more than 1 to 2.5 per cent of cases[34,42] and deaths are extremely rare with adequately controlled therapy.

Murray[36] has emphasized the usefulness of heparin administration in the patient with acute severe pulmonary embolism. He believes that propagation of thrombus material from the site of embolus lodgment may be avoided if anticoagulant administration is immediately started and the incidence of fatality due to the original acute episode thus reduced. De Takats[43] analyzed a group of patients who died from pulmonary embolus and concluded that 60 per cent live for a period of one hour to several days. If the cause of some of the delayed deaths from pulmonary embolism is the propagation of thrombus material in the pulmonary artery, a fertile field of endeavor is opened to the employment of anticoagulants. A recent report from the Massachusetts General Hospital[44] stated that thrombus formation proximal to the site of venous ligation was found in more than 50 per cent of a small group of medical pulmonary emboli cases who were treated by ligation and later examined at autopsy. These two preceding reports suggest that there is a rational basis for the employment of anticoagulants even as an adjunct to ligation. This subject was discussed in the Cornell Conference[29] and by Homans.[41]

In one analysis of cases[34] a fatal pulmonary embolus occurred in approximately 6 cent of patients with deep venous thrombosis and in 18 per cent of those individuals who had already experienced one non-fatal pulmonary embolus. The primary objective of all therapy employed in venous thromboembolism is the reduction of this particular mortality rate to the lowest possible figure. This result is being achieved equally well by anticoagulants and by vein ligation as attested by the statistics from both proponents.[16,29,34,35,36,38,40,42] The Columbia Clinic[28] analyzed the available over-all experience of many groups with anticoagulant management. It was determined that subsequent fatal embolism occurred in 0.3 per cent of 2,327 cases of deep venous thrombosis and in 0.9 per cent of 887 cases of initially non-fatal pulmonary embolism.

The troublesome complaints of the phlebitic patient months and years following the acute episode of phlebitis are familiar to most practitioners and have been considered in detail by Homans,[45] Bauer[46] and Buxton.[47] Bauer[46] reported a small group of patients with deep venous thrombosis localized to the leg below the level of the popliteal vein who were treated with heparin and investigated both pre- and post-treatment by phlebography. He noted that the level of venous occlusion did not ascend further once therapy was started thus avoiding compromise of the important, strategically located popliteal vein. As brought out in the Columbia Clinic,[38] Bauer, after a three-year follow-up, further observed a very marked difference in the incidence of both subjective and objective postphlebitic difficulties between the anticoagulant-treated group and a comparable series of patients receiving no active therapy. Similar evaluation of surgically managed patients is not available and is awaited by all interested clinicians.

Loewe's[16] observations on the dissolution of "sludge" thrombus material by heparin are important. This phenomenon may account for some of the remarkable improvement seen in extremities with acute venous thrombi shortly following initiation of anticoagulant treatment. It may also explain how a greater length of normal functioning vein is retained after the acute episode has subsided.

Surgical Therapy. Opponents of ligation have often stated their fears of troublesome edema and ulcers subsequent to ligation of such important venous channels. One earlier report[48] indicated that edema was present immediately following ligation in 80 per cent of common femoral and 45 per cent

of superficial femoral vein interruptions; edema was observed at a later follow-up period in approximately 40 per cent of both common and superficial femoral ligations. More recent reports make no mention of significant edema or ulceration after femoral vein ligation. The surgical proponents believe that ligation of the veins of the extremities does not produce difficulty in the circulatory dynamics and that complete block of the vessel up to the point of ligation does not necessarily occur. However, most reports on inferior vena caval ligation do remark on significant edema and even leg ulcerations[35] occurring shortly following operation.

Homans, who is generally considered to be the dean of the ligation school, has clearly stated[41] what he considers at the present time to be the indications for and preferred levels of ligation. It is to be emphasized that he regards vena caval ligation *only as a last resort* to be employed when repeated embolism has continued to occur despite peripheral venous ligation and/or adequate anticoagulant administration. His statement that certain forms of peripheral venous thrombosis, in which pulmonary embolism has not occurred, may be adequately handled by medical management reflects a change in viewpoint by the surgical school. Ligation of the femoral veins under local anesthesia is classed as a "minor" operation; however, ligation of the common iliac and especially of the vena cava are by no stretch of the imagination "minor" operations and are to be considered as surgical procedures of a definitely major nature. Even femoral ligations may be technically difficult in the obese patient or in an individual who has an edematous, swollen thigh such as may occur in congestive heart failure or ileofemoral venous occlusion.

The morbidity and total duration of hospitalization following ligation is reported to average eight days.[48] This is definitely less than the hospital stay of anticoagulant-treated patients. With the possible exception of the Swedish school schedules,[49] the medical programs of therapy extend the treatment period to at least ten days and usually average two weeks. Some clinicians extend the period of treatment as long as four weeks.[16,39] This point may well merit consideration in analyzing results and the practicability of a method of therapy, particularly in a crowded municipal hospital.

Medical Therapy. Loewe[16] has clearly and forcefully presented the case for heparin/Pitkin menstruum. He states that it has been possible to eliminate one of the greatest drawbacks of the menstruum, i.e., severe pain at the site of injection. Distressing discomfort accompanied almost each injection of the earlier product and forced discontinuance of treatment in many patients. Loewe states that 90 per cent of patients can now be satisfactorily and adequately managed (i.e., an adequate but safe elevation of venous clotting time achieved) with an average dose of 300 mg. every other day. This, if confirmed by other investigators, is of considerable practical aid to the physician who wishes to employ this form of treatment in general practice.

Murray[36] has supplemented his previous observations with another report on the successful use of the sodium salt of heparin by continuous intravenous infusion. A practical complaint concerning this mode of therapy is the difficulty of maintaining a continuous intravenous drip for a period of six to twelve days. Such prolonged venous therapy is difficult for the doctor as well as for the patient. This objection is not encountered with heparin/Pitkin menstruum or with a method of employing intermittent subcutaneous injection of the sodium salt of heparin. Dicumarol treatment also obviates this difficulty.

The cost of either heparin or heparin/Pitkin menstruum is many times that of dicumarol. This difference may be of practical importance to the physician who must treat a patient of modest means. It is equally pertinent to the administrative and professional hospital staff who are charged with deciding upon an effective yet economically reasonable method of handling thromboembolic disease. Although the ideal anticoagulant must be safe and reliable, it should also

be economically reasonable and readily available.

The Mayo Clinic report[34] on dicumarol is clearcut, fairly stated and instructive. Dicumarol is orally and therefore easily administered. Most groups employing dicumarol use supplementary heparin to obtain an immediate anticoagulant effect during the average forty-eight-hour lag period before adequate prolongation of the prothrombin time has been achieved by dicumarol. This program removes a main objection to the use of the slower acting dicumarol in acute thrombotic emergencies. Groups experienced with dicumarol believe that vitamin K and transfusion are more efficacious in combatting excessive prothrombin deficiency and hemorrhage than Loewe[16] indicates. As indicated by Wright[28] and the Mayo Clinic reports,[34] the prothrombin test should be in the hands of an experienced technician or closely supervised by a physician thoroughly familiar with the technic. Some investigators[50,51] believe that the dilute (12.5 per cent plasma) prothrombin time is more sensitive and a more accurate and safer guide to therapy than is the whole plasma determination. However, the dilute plasma test is more time consuming and errors of technic appear to be exaggerated. Most observers employing dicumarol[28,34,42] believe that the dilute prothrombin test is not necessary for safe control of dicumarol administration and that whole plasma prothrombin determinations carried out according to the modified Quick method suffice. A laboratory or physician who wishes to employ prothrombin determination tests for control of dicumarol therapy should make certain of the constant potency of the thromboplastin employed. Significant variations in results are produced by changes in the quality of thromboplastin, variations of such magnitude as to render the tests unreliable for the control of dicumarol treatment. In order to broaden the applicability of prothrombin time tests so as to enable a physician with only an occasional patient receiving dicumarol to control the treatment, some commercial firms are attempting to produce small kits complete with all materials necessary for the test. Wright[28] has described in detail a dependable technic for prothrombin determinations. Even so, if dicumarol treatment is to be made available for general medical practice, the greatest need is for a still simpler prothrombin test, preferably a bedside type more dependable than previous ones devised.[52]

Many groups experienced with anticoagulants [16,28,34,36,38,40,42,53] base their therapeutic dosage of heparin and dicumarol on the premise that continued elevation of venous clotting or prothrombin time is desirable. The Swedish anticoagulant group[49,54] initially assumed that heparin exerted beneficial effects in thromboembolism in some manner not currently understood and that the gross and generally unsatisfactory clotting time determination did not accurately measure this antithrombosing property. They believe that continual elevation of the venous clotting time need not be mandatory. According to their premise, intermittent intravenous injections of heparin at intervals of six to twelve hours should suffice to bring about such alterations of the blood coagulating mechanism as to effect satisfactory end results in thrombotic disease. They treated a large group of patients by the method of intermittent intravenous injection. The results in this series[29,49,54] compared favorably with any of the more customary medical or surgical methods. This is further evidence for the theory that anticoagulant drugs, at least the two principal ones, exert a common antithrombosing influence which is not accurately measured by present methods of clotting and prothrombin time tests. A recent preliminary report[55] by a group investigating this problem made observations on the electrical resistance of whole blood. Heparin was found to produce significant alterations in the electrical conductivity of whole blood, *in vivo* and *in vitro*, as measured by the resistance time. Some effect analogous to this may well be the common ground of action of anticoagulant drugs.

The dosage of heparin employed by the

Swedish group was much higher than customarily employed in this country and at the time of the reports occasioned some comment that doses of such magnitude could be given with impunity. Jorpes[54] inferred that the Swedish heparin was less potent than the American product. Wright[28] confirms these observations with specific data indicating that our heparin is approximately one-third more active than the Swedish. Anyone planning anticoagulant treatment on the Swedish principle should take cognizance of this significant difference in potency and adjust the dose accordingly. An even more practical modification of the Swedish plan is being tried at the Presbyterian Hospital.[56] The sodium salt of heparin is administered by intermittent subcutaneous injection at intervals designed to obtain elevation of the venous clotting time for only a portion of the period between injections. This method possesses the advantage that the drug can be administered without hospitalization of the patient thus eliminating the need for skilled venipunctures and close control of the venous clotting time. Such a departure from previous concepts of therapy can be judged properly only by the results in a large group of patients. These results must necessarily compare favorably with those obtained by continuous prolongation of venous clotting time.

Hemorrhage. Bleeding due to excessive anticoagulant effect must be carefully managed. The measures to be employed with hemorrhage secondary to prothrombin deficiency produced by dicumarol are generally effective.[34,57] When heparin produces bleeding, routine management consists of discontinuance of the drug and blood transfusion. Blood transfusion is used either for blood replacement or to return the clotting time toward normal. Protamine sulfate[58,59] in 1 per cent or 2 per cent solution administered intravenously returns the clotting time to normal within five minutes. The dose is usually 50 to 100 mg. of protamine sulfate. One mg. of heparin is believed to be neutralized by 1 to 2 mg. of the protamine solution. This preparation has been administered to humans[59] without untoward effects. Observations of the effect of protamine on the rate of bleeding are not available in the literature. The immediacy of action of the antidote for heparin would appear to be a definite advantage of heparin over dicumarol although further and more extensive clinical experience is needed in the use of protamine.

Symbathetic Block. It is believed that paravertebral lumbar sympathetic block[60] plays a definite though small rôle in the therapy of venous thrombosis. In the first place, acute thrombophlebitis of the deep venous system is encountered relatively infrequently. In one carefully studied series of combined venous thrombosis and pulmonary embolism,[42] acute inflammatory thrombophlebitis occurred in less than 10 per cent of the patients. Significant measurable arterial spasm secondary to acute phlebitis is rarely encountered. Thus, the situation indicating sympathetic block is not a common clinical problem. Furthermore, Loewe,[16] Murray[26] and others[42] have observed that anticoagulants allay vasospasm and the manifestations of the inflammatory phlebitis within a short time after starting therapy. However, it is generally agreed that severe pain in the extremities only partially relieved by the usual analgesics is definitely lessened following sympathetic nerve block. In addition, the persistent edema of an ileofemoral thrombosis frequently is rapidly reduced by this procedure. Most clinicians employ lumbar sympathetic block in the infrequent patient with acute inflammatory ileofemoral phlebitis. However, it is difficult to understand how paravertebral nerve block can prevent or reduce the incidence of pulmonary embolism. It would seem proper to consider such a measure as aimed only at symptomatic and objective improvement *in the extremity.* This would imply that whether or not nerve block is used one of the two specific methods for preventing pulmonary embolism is most assuredly indicated in acute thrombophlebitis of the deep veins. Emboli are encountered frequently enough

in patients initially presenting a picture of acute phlebitis to indicate specific therapy. Due to the technical difficulty of vein ligation below the level of the inferior vena cava in this type of case, anticoagulants appear to be the treatment of choice.

Local anesthesia also has a part in the management of the severe pleuritic pain subsequent to embolization. If the usual sedation measures are not successful, a procaine block of certain of the intercostal nerves frequently relieves the patient whose site of pleural irritation is located sufficiently lateral or anterior in the chest to allow proper local infiltration.

Phlebography has been referred to but twice in the Seminar, an indication of its present status. Loewe[16] expressed the current feeling of most American authorities that the procedure possesses several marked limitations: (1) The individual variation in normal venous channels makes interpretation difficult; (2) clinical diagnosis is usually possible without recourse to a rather complicated diagnostic procedure; (3) phlebography is time-consuming, not inexpensive and not without discomfort to the patient; (4) it entails moving the patient in a period when he should ideally be kept at strict bed rest and (5) the method is feasible only in hospitals where special facilities and experience in interpretation are available. Bauer initially used phlebography to establish the diagnosis of deep venous thrombosis. Recent reports from Sweden, however, indicate that even there phlebography is being employed much less frequently.

HEART DISEASE

Cardiac Infarction. Wright[28] has compiled an excellent summary of the present status of anticoagulant therapy in heart disease. The currently published opinions and preliminary reports indicate that the introduction of anticoagulants appears to diminish thromboembolic complications which add to the morbidity and mortality of cardiac infarction. The reports of Ogura[10] and Meyer,[11] indicating accelerated coagulability of the blood during the early days of a cardiac infarction, provide additional basis for prophylactic measures to avoid thrombotic phenomena. The clinical experiences of physicians, who in years past have not infrequently observed complicating thrombotic and embolic episodes in the course of an otherwise uneventful cardiac infarction, are added confirmation of the logic of this new therapy.

It is believed that embolic phenomena from mural thrombi and peripheral venous thrombosis will certainly be reduced and further extension of the area of myocardial infarction prevented. Wright particularly has observed beneficial effects in stopping recurrent and progressive infarction. The conclusions of the extensive study of the American Heart Association will be eagerly awaited by all physicians. In the meantime, many are employing the anticoagulants in their own practice after having thoroughly considered the pros and cons of their use. In the light of the long period during which these drugs are administered (four to eight weeks), the inexpensiveness of dicumarol would appear to offer a real advantage over any form of heparin management. The advantages of immediate heparinization at the start of dicumarol therapy are debatable. However, it seems logical to obtain the antithrombosing effect as soon as possible. Fresh mural thrombi may be found at autopsy as early as twenty-four hours following onset of symptoms of infarction.[61] Administration of this preliminary heparin may be satisfactorily accomplished with either heparin/Pitkin menstruum or by repeated intravenous or subcutaneous injections. The continuous intravenous drip is obviously best avoided in those situations when cardiac reserve may be substantially impaired.

A word of caution is indicated concerning the occasional case of dissecting aneurysm of the aorta which may be confused with cardiac infarction. If there is a reasonable suspicion of an aortic dissection, the start of anticoagulant therapy should await work-up and further observation. Patients with cardiac infarcts did manage to survive in great number in the days prior to the intro-

duction of anticoagulants and these drugs are not quite the most suitable treatment for an aorta in the process of dissection.

If a pulmonary embolus occurs in a patient convalescing from a cardiac infarction not being treated with anticoagulants, that patient should be managed like any case of pulmonary embolus, either by the use of anticoagulants or by peripheral venous ligation. The tendency of physicians is to ascribe to a mural thrombus the source of any embolus occurring in an individual with recent cardiac infarction. Carlotti et al.[44] recently analyzed an autopsied series of a medical (predominantly cardiac [70 per cent]) group of patients with pulmonary embolism. The heart was found to be an infrequent source of the embolus (11 per cent), the source of which was usually (78 per cent) in the peripheral deep veins. It would thus seem that a cardiac patient in whom embolism to the lungs occurs should either have his peripheral veins ligated or receive anticoagulants even though no clinical evidence of deep venous thrombosis is present in the extremities. The early mortality in this series[44] of pulmonary emboli was 28 per cent in those treated by vein ligation compared to 50 per cent in those who received no specific treatment. This significant difference is proof that proper management reflects itself in a lower mortality rate. It would appear, however, that administration of anticoagulants is more convenient than ligation, particularly in those patients without evidence of peripheral venous occlusion.

Emboli from Intracardiac Thrombi. Wright's[28] results with anticoagulant treatment in patients with chronic fibrillation and embolic phenomena are encouraging and noteworthy. The accepted custom of sitting idly by while repeated emboli occur may now be discarded. Certainly an embolus occurring in a fibrillating cardiac, whether to the systemic or pulmonic circulation, is an indication for proper and profitable use of anticoagulants. Propagation of fresh thrombus material at the site of lodgment of the embolus will be prevented as well as further thrombus formation in the auricle or ventricle. The prolonged dicumarol treatment suggested by Wright must necessarily be conducted with the usual individual on out-patient status. Wright's experience with ambulatory dicumarol therapy indicates that it is practical although the inability to control dosage closely makes it more dangerous than when carried out within a hospital. Ambulatory dicumarol administration has also been conducted successfully by Nichol,[62] Peters[6] and Putnam.[63] Against this experience must be countered the sobering statement from the Mayo group[34] that ambulatory dicumarol therapy is inadvisable unless controlled by prothrombin determinations done at frequent intervals. It would appear that a decision to institute ambulatory anticoagulant treatment should be based on a careful consideration by doctor and patient of the potential risks of each alternative, i.e., bleeding versus embolism to a vital area. Dicumarol obviously has manifold advantages over heparin for this type of prolonged ambulatory therapy.

Subacute Bacterial Endocarditis. Wright[28] expressed the opinion, which seems to be generally held with the possible exception of Loewe,[64] that anticoagulants are ineffective in subacute bacterial endocarditis except when there is embolic occlusion of a large artery. Recent reports[65–69] from clinicians who have intensively studied this problem conclude that the crux of the efficacy of therapy in bacterial endocarditis lies in the principle of adequate dosage of antibiotics over sufficient periods of time. They believe that anticoagulants are not necessary adjuncts. The ability of penicillin to penetrate fibrin[70] may partially explain the difference between the effectiveness of treatment with antibiotics today and that of five years ago with the sulfonamides. The sulfonamides do not possess this fibrin-penetrating characteristic. It would appear that anticoagulant therapy does not contribute enough to the cure of the infection to warrant the added danger of sustained hemorrhage from ruptured mycotic aneurysms or from the gen-

eral vascular fragility in this disease. The expense of the drugs and the tests necessary for the proper and safe control of administration are minor but definite added considerations. The discomfort to the patient of additional venipuncture or hypodermic injection is not negligible.

MISCELLANEOUS PROBLEMS OF THROMBOSIS

Arterial Occlusion. The introduction of the aggressive use of heparin and dicumarol in the management of acute peripheral arterial occlusions constitutes an exceedingly important and relatively new addition to our therapeutic armamentarium for the handling of such emergencies. To those with considerable experience in managing such problems surgical intervention in the form of embolectomy or thrombectomy has been far from satisfactory, due partly to difficulties in the localization of the exact site of occlusion, to frequent reforming of a thrombus at the site of incision and to the intense arterial spasm not infrequently incited by operation. The Mayo Clinic[34,71] is particularly encouraging in their recent reports on the conservative method using anticoagulants plus measures to alleviate reflex vascular spasm. The still all important element of time in relation to the delay between vascular occlusion and initiation of therapy is emphasized by the Mayo statistics.[71] When treatment was initiated twenty-four hours or longer after the occurrence of the embolic occlusion, ischemic necrosis occurred in 90 per cent of the patients but in only 25 per cent when treatment was started earlier. In arterial thrombosis, ischemic necrosis occurred in 80 per cent of patients when treatment was started more than twenty-four hours after onset but in only 50 per cent when appropriate measures were initiated earlier. The precise situation in which surgical intervention is indicated is difficult to define. It is accepted that embolectomy may be the treatment of choice in certain situations. It is only fair to believe that the results of surgical thrombectomy will be definitely improved by employing concurrent anticoagulant treatment pre- and postoperative. However, at present it is believed that a trial of medical treatment is proper for at least eight to twelve hours before performing surgical procedures. An immediate antithrombosing effect is obviously best accomplished by some form of the immediately-acting heparin. After the first one to three days either dicumarol or heparin will be found adequate for maintaining the altered state of blood coagulability. Reflex arterial spasm should be alleviated by papaverine and/or an appropriate form of regional anesthesia. A pharmacologic block of the sympathetic ganglia may be attempted by agents such as tetraethylammonium[72,73] but further evaluation of these drugs in such acute situations is necessary before entire reliance is placed upon them.

Frostbite Gangrene. The problem of frostbite gangrene has been intensively studied by Lange and his associates.[74] They have observed that red cell "sludge" forms in the capillaries following exposure to severe degrees of cold. The ischemic necrosis secondary to frostbite presents the histopathologic picture of a thrombotic process due to red cell agglutinative thrombi in the small vessels. If animals or human volunteers were heparinized as late as forty-eight hours following exposure and the anticoagulant therapy continued for seven to nine days, ischemic necrosis and massive gangrene were prevented; within this time, tissue death consistently occurred in the control animals or humans. These observations and their therapeutic implications are obviously of significant practical import to physicians who encounter this civilian and military hazard. The introduction of this mode of therapy is the first logical and effective advance in the management of a hitherto very unsatisfactory therapeutic problem.

CONCLUSIONS

It is clear from the reports that have appeared in these Seminars on Thromboembolism that there are available at present two extremely effective methods of therapy for venous thromboembolic disease. The various forms of heparin and dicumarol

therapy should be considered complementary rather than alternative modes of treatment. Vein ligation is an alternative to medical therapy whenever it appears unfeasible to carry out an adequate program of anticoagulant management. In like manner, when surgical therapy is the favored treatment, anticoagulants should be considered as the alternative method and should be instituted whenever vein ligation is not practical. Either medical therapy with anticoagulants or surgical vein ligation should be carried out as an emergency procedure in every case of deep venous thromboembolism.

The ultimate decision as to the most efficacious management of thromboembolic problems must be deferred until critical follow-up studies on sufficiently large groups of patients become available.

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Combined Staff Clinics

Thromboembolism

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, N. Y. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. YALE KNEELAND, JR.: The subject of today's clinic is indicated by that new double-barreled word "thromboembolism" and like the word the subject itself in a sense is new. A standard textbook of surgery published in 1936, only eleven years ago, characteristically dismissed the subject in two or three sentences. The statement was made that pulmonary embolism sometimes occurred following surgical operations and that it was a dangerous complication, not infrequently fatal. Thrombophlebitis was stated to be a disease of the lower extremities characterized by pain and swelling and treated by bed rest with elevation of the limb. One had the impression in those days, only a decade ago, that thromboembolism in its various manifestations was an act of God about which very little could be done and it was more pleasant not to think too much about it. That situation has now changed. In introducing the newer aspects of the subject, I should like to call first upon Dr. Cross to discuss briefly the pathogenesis, mechanisms and clinical symptoms and signs of thromboembolism.

DR. RICHARD J. CROSS: Not much is known about the underlying pathology of thromboembolism. Apparently, most cases are associated with an abnormality in the clotting mechanism. Certain modifications of our routine tests reveal that the blood of these patients tends to clot a little more readily than that of patients with normal blood; however, this finding has not been correlated with what is known about the clotting mechanism and we cannot state just what the abnormality is.

Certain predisposing factors are known. Of major importance is venous stasis. While venous thromboses do occur in otherwise healthy individuals who have been enjoying full activity, the majority of cases develop in people who have been confined to bed, particularly in elderly or cachectic individuals with poor muscle tone. Tissue damage is apparently another precipitating factor in many cases. It may be that the damaged tissue releases a thromboplastic substance which gives rise to the above mentioned abnormality of the clotting mechanism.

It has recently been shown that the site of origin of venous thromboses is usually in the muscular branches of the deep veins of the calf or in the plantar veins of the foot. Involvement of other veins occurs rarely.

There are some authorities who believe that the foregoing remarks should be limited to those patients with venous thrombosis in whom there is very little inflammatory response. They refer to these as "phlebothrombosis," while the others with a widespread inflammatory reaction are referred to as "acute thrombophlebitis" and are believed to be due primarily to an inflammation of the vein wall of unknown etiology with clotting a secondary phenomenon. However, in our experience the majority of cases fall between these two extremes and the picture may shift from one to the other as I shall show you shortly.

Let us now consider the different phases in the formation of a thrombus in a muscular branch of the deep venous system of the calf, attempting to correlate the pathology with the symptoms, signs and laboratory findings.

(Table I.) The thrombus probably starts as a layer of platelets on which a clot forms, the end of the clot being carried up proximally by the flow of the blood. At this stage there is no obstruction of any vein. There is no inflammatory response and there are no symptoms, signs or laboratory findings.

TABLE I
VENOUS THROMBOSIS; SYMPTOMS, SIGNS AND LABORATORY FINDINGS AT DIFFERENT STAGES

A.	None
B.	Calf fullness
	Tenderness over veins
	Positive venogram
C.	"Dead" feeling
	Swelling
	Positive Homans' sign
	Fever
	Leukocytosis
	Elevated erythrocyte sedimentation rate
D.	Severe pain
	Extreme tenderness
	Marked swelling
	Pallor
	Absent pulses
E.	Ankle edema
	Palpable vein

The clot grows until it occludes the vein and we might then anticipate that there would be edema in the muscle which is drained by that vein. This is apparent clinically by a feeling of fullness in the calf muscles so that the affected calf feels more firm and less flabby than the other. We have found this sign to be the most reliable evidence of an early thrombosis. In addition, there is often a slight inflammatory response in the vein wall where the clot first formed. This, as might be anticipated, will give rise to a localized area of tenderness in the calf noted in almost all of our patients although more difficult to interpret since it is not an objective finding. The only other procedure which might help us to make the diagnosis at this early stage is a venogram. This is performed by the injection of radio-opaque material into an ankle vein, followed immediately by x-rays of the leg. These films are studied to see if the deep venous system fills completely. This procedure has been used quite widely in Sweden but most of the workers in this country who have tried it have not found it satisfactory because they cannot differentiate thrombosis from failure to fill because of venous spasm or other factors.

The thrombus also grows proximally, forming a "red tail" which waves freely in the blood stream extending up into the larger venous channels. This causes neither disturbance of the circulation nor inflammatory response and we usually remain unaware of its presence unless a piece breaks loose and forms a pulmonary embolus.

Later, the lower part of this "red tail" becomes adherent to the walls of the larger veins, causing a more widespread and intense inflammatory reaction. The patient may have some pain but more commonly at this stage he complains of a feeling of discomfort in the calf, a 'heavy' or 'dead' feeling. There is now obstruction of some of the main veins and because of this and of the inflammatory response there will be some swelling of the calf as a whole as evidenced on inspection or, more precisely, by measurement. In addition, the inflammatory response will result in a positive Homans' dorsiflexion sign: on passive dorsiflexion of the foot there is pain in the calf. If the inflammatory response is intense enough, there will obviously be fever, leukocytosis and an elevated sedimentation rate. These have been stressed as diagnostic aids but we have not found them of great value. They are roughly correlated with the amount of inflammation present and we believe that the signs I mentioned earlier are more valuable evidence thereof.

As the waving "red tail" grows proximally, its area of attachment to the vein wall may also extend up the leg causing intense inflammation in the popliteal, femoral and iliac veins. At this stage there is often severe pain and extreme tenderness with redness and marked swelling, due not so much to venous obstruction as to the intense inflammation. In a few of these cases there is a reflex vasospasm which results in pale, cold extremities with absent pulses giving the typical picture of arterial occlusion. This is the syndrome which is described by Ochsner and others as the "acute thrombophlebitis" to which I re-

ferred earlier but we have seen it develop in the general fashion which I have described. At this stage there is far less danger of pulmonary embolism because the inflammatory response fixes the clot to the vein wall and it is a common clinical observation that "acute thrombophlebitis" is far less apt to be followed by pulmonary infarction than is benign "phlebothrombosis" with few or no signs.

The final stage occurs when the thrombus has become organized and when all exposed surfaces have become covered with a layer of endothelium. At this time embolism is impossible and there is no reason to anticipate fresh thrombus formation. There will often be a certain amount of ankle edema on a mechanical basis. This will usually clear as collateral circulation takes over in the course of the next few months. Depending upon how superficial the vein and how good the muscle tone, one may or may not be able to feel the thrombosed vein as a hard cord.

It is important to realize that although I have described this process in separate stages, it actually develops continuously. The distal part may be completely organized while the free "tail" is still growing proximally. Since abnormal findings depend upon the amount of venous obstruction and inflammation present, they give us no indication of how much free clot may have formed and it is all too common for fatal emboli to break loose from leg veins without giving rise to any of the symptoms, signs and laboratory findings I have described. There are no precise data available as to the time factors involved and these are probably quite variable but there is some evidence that any given segment of a thrombus becomes fixed to the vein wall within five days of its formation; and if growth of the thrombus can be prevented, that which is present will probably be endothelialized completely within ten to twelve days.

Next I should like to discuss the signs and symptoms of pulmonary embolism. Obviously, they will depend upon the size of the embolus. A small embolus may cause transient damage only, without infarction, while a massive one may completely occlude the pulmonary artery. In general, the small emboli go out to the periphery of the lung and cause an inflammation of the pleura with resulting pleuritic pain, a symptom which we found in almost all of our patients. A larger embolus will tend to give a more intense pleuritic response, reflex changes and, therefore, dyspnea. As the result of the damage to vessel walls, there will be exudation of fluid and crepitant râles will be heard. That is the most reliable physical sign of pulmonary embolism which we have found. If you listen persistently and repeatedly, you will often succeed in putting your stethoscope over the area of pleura involved and hear a friction rub. In the case of left lower lobe infarcts this rub may have a pericardial element. At a later stage there will be consolidation with the physical signs thereof and characteristic x-ray findings. However, if the infarct is not large, the chest x-ray is often entirely normal particularly in the early stages. If any abnormalities are found, they usually consist of indefinite hazy shadows; the classical wedge-shaped shadow which is described in the literature has been rarely encountered by us. Pleural effusion occasionally occurs as a result of this pleurisy, a fact which should be borne in mind in considering the differential diagnosis of pleural effusion. If there is a sufficient area of the lung involved, there will, of course, be fever, leukocytosis and an elevated sedimentation rate. (Table II.)

With large infarcts the picture is often quite different. The large embolus does not approach the periphery of the lung but is stopped near the hilum. We have seen several patients who complained of a nonpleuritic, deep, visceral type of pain, presumably mediated through the autonomic nervous system, which was followed a day or two later by pleuritic pain; this we interpret to mean that the infarcted area has spread out to the periphery. Such patients often appear critically ill with marked cyanosis and severe dyspnea. Cough, however, is relatively rare and the hemoptysis described in most textbooks is, in our experience, even

rarer. The obstruction to one of the main branches of the pulmonary artery will obviously cause hypertension in the lesser circuit. It may be noted that the pulmonic second sound is louder than it was before. Occasionally, there are electrocardiographic changes, both because of the changes in pressure and also on the basis of autonomic reflexes. The pulmonary hypertension may be severe enough to cause acute heart failure. Should the diaphragmatic pleura be involved, there may be abdominal signs with spasm and rigidity in the upper abdomen. Jaundice has been reported to be caused by pulmonary infarction but so far we have not observed it. Finally, of course, there may be massive emboli with death within a few minutes.

TABLE II

PULMONARY EMBOLISM; SYMPTOMS, SIGNS AND LABORATORY FINDINGS WITH EMBOLI OF DIFFERENT SIZE

A. Very Small Emboli
   None
B. Small Emboli
   Pleuritic pain
C. Medium Emboli
   Dyspnea
   Râles
   Friction rub
   Signs of consolidation
   X-ray shadow
   Pleural effusion
   Fever
   Leukocytosis
   Elevated erythrocyte sedimentation rate
D. Large Emboli
   Non-pleuritic pain
   Severe dyspnea
   Cyanosis
   Cough
   Hemoptysis
   Loud pulmonic second sound
   Electrocardiographic changes
   Acute right heart failure
   Abdominal signs
   Jaundice
E. Massive Emboli
   Death

It must be obvious to all of you that pulmonary embolism may cause a clinical picture very similar to that of pneumonia, myocardial infarction and many other conditions. Differential diagnosis is essentially an individual problem and cannot be solved by any general rules. In my opinion, the one unforgivable sin is also the most common one, namely, failure to keep the possibility of pulmonary embolism constantly in mind, especially when faced with some atypical pulmonary condition.

STUDENT: How often are fever and tachycardia the first evidence of thromboembolism?

DR. CROSS: In our experience, it is unusual to find fever caused by venous thrombosis in the absence of any local evidence of inflammation, even though that evidence may first be discovered in the course of a complete examination of a patient with unexplained fever. However, it is entirely possible to have a small pulmonary infarct deep in the lung which will give no evidence of its presence except by fever, tachycardia and tachypnea.

DR. KNEELAND: With this admirable clinical background for the conditions under discussion, we would now like to present to you two cases. The first, I shall present in the form of a brief abstract of the clinical record of a patient admitted here in October, 1944, just two and one-half years ago. This patient was a motorcycle policeman thirty-four years of age who entered with the chief complaint of chest pain, pleuritic in character, of two and one-half weeks' duration. It was noted on taking the man's history that he described an injury to his knee sustained while roller skating about eight weeks before admission. This had been sufficiently severe to incapacitate him with pain and swelling of the knee for a few weeks. Then he went back to duty, presumably to his former occupation of riding a motorcycle, the mechanics of which have an obvious bearing on what is to follow.

Two and one-half weeks before admission, he had had a sudden pain in the right chest, pleuritic in character. His local physician put him to bed and gave him a few doses of sulfadiazine on which he improved. After a week he was well enough to want to go back to work but his physician made him stay at home. Four days before admission here, he had an x-ray picture taken which showed fluid in the right chest; then on the following day he had a new bout of

pleuritic pain, again in the right lower chest and for the first time he noticed blood in his sputum. He had had no chills, no fever, very little cough and little shortness of breath.

On admission here he was found to be slightly cyanotic and slightly short of breath. His heart rate was 110. He had signs of a small amount of fluid in both pleural cavities and this was substantiated by x-ray examination. His white count was 10,000 with 72 per cent polymorphonuclears. In addition to the small effusion in both pleural cavities, there was a shadow in the right lower lung field. He was treated for pneumonia with full doses of sulfadiazine. Seven days later, after an uneventful clinical course, the patch in the lung had disappeared almost completely and further absorption of the fluid had taken place. On the tenth hospital day, when apparently fully recovered, he suddenly sat up in bed, gasped, turned very pale and then cyanotic and died of respiratory failure in twenty minutes. At autopsy extensive phlebothrombosis of the lower extremity was found together with old and fresh massive pulmonary infarction.

This case is presented to serve as a basis for comparison with the next case which Dr. Pons will present.

DR. EDUARDO R. PONS: Mr. D. B. is a fifty year old post office clerk who was born in the British West Indies. His past history is irrelevant, except for the fact that he has had varicose veins for many years and that seven years ago he had a superficial and deep thrombophlebitis of his right leg with subsequent mild residual edema.

A month ago he was admitted to the urologic service with symptoms of chronic urinary obstruction. A work-up revealed a median bar hypertrophy. Three weeks ago he had a transurethral prostatectomy from which he convalesced uneventfully. Early ambulation was carried out. On the fifth postoperative day, he noted a mild pain in his right lower leg and a sense of fullness in the right calf. He was nevertheless sent home on the sixth postoperative day and returned to the regular follow-up clinic in urology a week later. At the time he had no urinary complaints but did complain of some pain in his right lower leg. He was then referred to the varicose vein clinic at which time an induration and tenderness over the right saphenous vein in its course over the lower leg was found. His pain had diminished in the week since discharge so he was considered to have a subsiding thrombophlebitis of a superficial vein and he was sent home to bed and told to wear an Ace bandage. The next day he suddenly experienced a sharp pleuritic pain in his right lower chest, without cough, without fever and without any symptoms of an upper respiratory infection. The pain persisted for three days after which he began to have fever with occasional spikes to 103°F. At the onset of fever, he was seen by his private physician who gave him penicillin, 300,000 units intramuscularly, every day for three days without any improvement of symptoms. In view of this lack of response, he was referred to the Presbyterian Hospital as a case of penicillin-resistant pneumonia. On admission one week ago, he appeared acutely ill and was mildly dyspneic. His temperature was 100.4°F. There were signs of extensive consolidation over the right lower lobe and right middle lobe, with dullness, egophony and classical tubular breathing. There were also a few râles at the left base. Chest x-ray confirmed the clinical impression of marked consolidation in the lower right lung and also showed some increased density in the left base.

On the ward the previous findings in the lungs were confirmed. In addition, he was found to have superficial tenderness and induration over the course of the internal saphenous vein on the right and also a sense of fullness in the right calf.

A review of the sequence of events, beginning with his postoperative leg pain and leading up to the presenting picture, justified a diagnosis of pulmonary infarction secondary to embolization from superficial and/or deep thrombophlebitis in the right lower leg. He was, therefore, started on

anticoagulants and penicillin was given prophylactically for secondary pulmonary infection of the infarcted area. His course in the hospital has been uneventful. During the past four days he has been asymptomatic and afebrile. The physical signs have changed slightly in that he now has minimal signs of fluid at the right base. The sputum, blood, and nose and throat swabbings have all been studied bacteriologically and have been found to be negative.

DR. KNEELAND: I should like to call your attention to the marked general similarity between these two cases. In each there was a disturbance of the lower extremity. In Case D. B. there was a fairly good clinical picture of thrombophlebitis and in the first case at least an injury. In each instance there was a long latent period. In each case there was a sudden development of pleuritic pain. The symptoms as described are almost superimposable. In each instance the patient was treated at home for pneumonia by his physician; in each instance he was sent to the hospital because of failure to respond to treatment and in each instance there was fluid in both pleural cavities and consolidation in the right lung as well. In the first instance, unhappily, the true diagnosis was not suspected; the patient was allowed to continue on routine treatment for a hypothetical infection of the respiratory tract and after a period of ten days in the hospital a final, massive, terminal embolization took place. The second patient, however, although admitted for pneumonia, was immediately recognized as a probable case of pulmonary embolism and the moment he arrived on the ward appropriate therapy was instituted. His course has been uneventful and he made a complete recovery.

The second case has been treated according to the methods employed by the group studying thromboembolism in this hospital. Dr. Cosgriff will now discuss these methods for treatment of thromboembolism by anticoagulants.

DR. STUART W. COSGRIFF: Thromboembolism posed a difficult problem in the days of conservative or expectant observation therapy. If the patient was kept active and walking around there was a real danger of "fracturing" the thrombus which was present in the vein, thus producing a pulmonary embolus; on the other hand, if he were put to bed and kept quiet, there was an equally real possibility of adding to the propagation of the thrombus in the legs and thus building up more potential pulmonary emboli. Anticoagulant therapy has attempted to overcome this dilemma.

One of the first questions to be asked when considering anticoagulant therapy is: What is the basis for and what are the therapeutic objectives of anticoagulant therapy in thromboembolism? The aim of anticoagulant therapy is to modify the general blood coagulation mechanism of the body so that further propagation of the thrombus in the affected vein is halted and opportunity thus given for the natural inflammatory mechanism to fix the thrombus firmly to the vein wall. It has been demonstrated experimentally that between the second and fifth day a bland thrombus in an intact vein will become quite firmly attached so as to preclude embolization; that is the theoretical basis for our therapy. If pulmonary embolization has occurred, treatment aims also to prevent further propagation of the thrombus at the site of lodgment of the embolus in the lungs and more extensive lung tissue infarction.

There are several schools of anticoagulant therapy. One group advocating heparin aims at a continuous elevation of the venous clotting time. This is accomplished either by a continuous drip of heparin over a number of days or by repeated subcutaneous or intravenous injections of heparin at intervals, usually of three or four hours. The second heparin group is the Swedish school. They consider that heparin exerts some effect which we do not measure with the venous clotting time and that intravenous injections of heparin during a twenty-four-hour period produce an adequate anticoagulant effect even though the clotting time undoubtedly is not prolonged during this entire period. Another group employs

heparin in Pitkin's menstruum (a combination of glycerin, acetic acid and dextrose) which gradually releases heparin into the circulation over a period of hours. Each injection is usually intended to prolong the clotting time adequately for approximately forty-eight hours.

Dicumarol is frequently used as an anticoagulant. When employed alone, there is a lag period of approximately thirty-six to forty-eight hours before an effective prolongation of the prothrombin time is observed. Therefore, the usual therapy is to employ both heparin and dicumarol. The main drug is dicumarol, heparin being used during the first thirty-six to forty-eight hours for its immediate anticoagulant effect.

As regards the anticoagulant mechanism of heparin, it acts as an antithrombin, as an antithromboplastin, probably also as an antiprothrombin and finally it decreases the platelet agglutinability in the blood. Dicumarol also acts first and foremost as an antiprothrombin. Recent work indicates that it also exerts an antithromboplastin effect and that it decreases platelet agglutinability. Probably these two anticoagulant drugs exert further effects in a manner which we do not understand and do not measure by our present methods. For instance, dicumarol produces an effective anticoagulant response, as measured clinically and by the prothrombin time, although there is only an inconstant and irregular prolongation of venous clotting time. In like manner, heparin produces an adequate elevation of venous clotting time without necessarily prolonging prothrombin time.

The aim of anticoagulant therapy is the energetic treatment of the thrombosis which is already present and the embolism which may have already occurred; secondly, and more particularly, the prevention of further thrombotic and embolic episodes. We must be alert to diagnose and treat the small and relatively asymptomatic thromboses and infarcts as well as the extensive ones, to recognize cases early and to prevent the repetition of embolic phenomena which so often cause death in pulmonary embolism. Of course, many of these patients with small pulmonary emboli recovered in the old days without any treatment but there were a substantial number who did not get better, who had repeated embolic phenomena culminating in a final fatal pulmonary embolus. Repeated embolization ending fatally is precisely what we are out to avoid with anticoagulant therapy.

DOCTOR: What are the expected complications and end results of venous thrombosis and of pulmonary embolus not immediately fatal?

DR. COSGRIFF: We have gathered some statistics from the American and European literature. It should be emphasized that the statistics for complications and mortality under conservative therapy are not directly comparable to the statistics for results of anticoagulant therapy. We are diagnosing venous thrombosis, particularly phlebothrombosis, and also pulmonary emboli much more frequently than we did five years ago. A number of these mild cases doubtless would do well under any therapy; however, it is my feeling that there may be an actual as well as an apparent increase in thrombotic disease during recent years.

Reports from American and European sources (Table III) comprising over 4500 cases of venous thrombosis indicate that approximately 21 per cent had subsequent thrombosis, 29 per cent had subsequent pulmonary embolus and 14 per cent had a subsequent fatal embolus. In the American group, considered separately, 900 cases under conservative treatment showed 12 per cent having subsequent thromboses, 19 per cent subsequent pulmonary emboli and 6 per cent subsequent fatal emboli.

We have studied thirteen reports (Table III) of the treatment of venous thrombosis with heparin and/or dicumarol. Of the total number of approximately 2200 cases under anticoagulant therapy, 1.1 per cent had a subsequent thrombosis, 1.2 per cent had a subsequent pulmonary embolus and 0.3 per cent had a subsequent fatal embolus.

Since we started our study at the Presbyterian Hospital (Table III), sixty cases of venous thrombosis have been treated. Subsequent thromboses have occurred in 3 per cent of those cases, pulmonary emboli in 1.7 per cent but no fatal emboli have occurred since treatment has been inaugurated.

mately 18 per cent of those cases. The Mayo Clinic reported 670 cases in greater detail showing that further thromboses occurred in 14 per cent, a subsequent pulmonary embolus in approximately one-third of the cases and a subsequent fatal pulmonary embolus in 18 per cent; that is, roughly one of

TABLE III
VENOUS THROMBOSES

	Number of Cases	Percentage of Cases Developing		
		Subsequent Thromboses	Subsequent Pulmonary Emboli	Subsequent Fatal Pulmonary Emboli
Conservative Therapy				
Total cases	4580	21	29	14
American cases	897	12	19	6
Anticoagulant Therapy				
Total cases	2267	1.1	1.2	0.3
Presbyterian Hospital cases	60	3	1.7	0

TABLE IV
NON-FATAL PULMONARY EMBOLI

	Number of Cases	Percentage of Cases Developing		
		Subsequent Thromboses	Subsequent Pulmonary Emboli	Subsequent Fatal Pulmonary Emboli
Conservative Therapy				
Total cases	822	....	....	18.5
Mayo Clinic cases	678	14	30	18
Anticoagulant Therapy				
Total cases	817	1.1	1.1	0.9
Presbyterian Hospital cases	80	2.5	3.8	1.3*

* One patient who died of massive fatal embolus ten minutes after the start of treatment.

I would like to draw your attention to the marked difference between the figures for mortality as given in Table III for the two different methods of treatment, conservative and anticoagulant. There has been a significant decline in the incidence of fatal pulmonary emboli since the inauguration of anticoagulant therapy.

As regards individuals who have experienced one or more non-fatal pulmonary emboli (Table IV) under conservative therapy, a fatal embolus occurred in approxi-

five people who had one pulmonary embolus which was non-fatal died of a subsequently fatal pulmonary embolus.

There are reports available on the use of anticoagulants in a total of 817 cases. Subsequent venous thrombosis occurred in 1.1 per cent, and subsequent non-fatal emboli in 1.1 per cent, subsequent fatal pulmonary emboli occurred in 0.9 per cent. At the Presbyterian Hospital we have employed anticoagulant therapy in eighty cases of pulmonary emboli with subsequent venous

thrombosis noted in 2.5 per cent and a subsequent pulmonary embolus in 3.8 per cent of the cases. One fatal pulmonary embolus occurred after the start of treatment, an incidence of 1.3 per cent.

There is a group of individuals in whom the possibility of thromboembolic phenomena appearing is much greater than in normal persons, namely, those with a previous history of thromboembolism, those with extensive varicosities, in cardiac disease, in some cases of carcinoma and after some abdominal operations. It is believed that the prophylactic use of anticoagulants is sound procedure when such individuals are postoperative or are subjected to enforced bed rest for some time because of fractures or medical conditions such as cardiac failure or infarction. In those subjects with a previous thromboembolic history, the risk of fatal embolism was determined by the Mayo group to be approximately 10 per cent. They have reported sixty-one such cases treated prophylactically without embolic phenomena and we have employed such measures in fifteen cases with similarly satisfactory results.

The Swedish investigators, in particular Bauer, have studied comparable groups treated under the previous "expectant observation" regimen and under heparin management. The clinical diagnosis in these patients was confirmed by venography with particular attention, after a three-year follow-up period, to the postphlebitic syndrome: swelling, edema, skin induration, skin atrophy and leg ulcers. Bauer found that practically 100 per cent of those patients who had been treated by conservative therapy had swelling of the affected leg while only about one-quarter of the heparin-treated group had swelling of the leg; that approximately 75 per cent of the conservatively treated group had some degree of trophic skin changes and induration, one-quarter of them having very marked trophic changes. The heparin-treated group showed none of these skin changes. With regard to ulceration of the lower legs, 20 per cent of the conservatively treated group had leg ulcers at three years. There were no leg ulcers in the heparin group at the three-year follow-up period.

DR. FRANKLIN M. HANGER: Dr. Cosgriff, would you tell us exactly how your group advises that thrombotic or embolic cases be managed?

DR. COSGRIFF: The program of management of a case of thrombosis or pulmonary embolism at the present time may be outlined as follows: The patient is placed in bed on strict bed rest for approximately six days. Anticoagulants are started immediately. If on the sixth or seventh day the patient is in good condition, the vital signs are normal and the pulmonary status as well as the leg signs are satisfactory, the patient is ambulated progressively, still maintained on anticoagulants. If by the twelfth or thirteenth day the patient is completely ambulatory, seems to be doing well and the signs of active venous thrombosis have cleared anticoagulant therapy is discontinued. With dicumarol there is a lag period of several days before the prolonged prothrombin time returns to normal so that an anticoagulant effect will persist for this period. Approximately by the fourteenth or fifteenth day the prothrombin time is within normal limits, the patient is completely mobilized and is released from our management.

We use a combined heparin and dicumarol program, with dicumarol as the principal drug. Since dicumarol usually has a twenty-four to forty-eight-hour lag period, heparin is employed during this preliminary period to obtain an immediate anticoagulant effect at the start of the dicumarol treatment and also at any time during the course of dicumarol treatment when the prothrombin time elevation drops below what we consider an effective level. At such times we give supplementary heparin for twelve to twenty-four hours until the prothrombin time elevation is again satisfactory.

Dicumarol is given orally, once daily. The first dose is 300 mg. On the second day the patient usually receives 100 or 200 mg. The average daily maintenance dose is usually 50 or 100 mg. This is given *only after the*

daily prothrombin time has been determined and the results reported to the physician responsible for anticoagulant regulation. The rectal route of administration has been investigated here and three or four patients have been treated in this manner with successful results. However, the usefulness of that route of administration needs more confirmation.

As determined in the laboratory of the Presbyterian Hospital, the prothrombin time normally is 14 (± 2) seconds. An elevation to 22 seconds, which is 30 per cent of normal prothrombin activity, is believed to be the level above which further intravascular thrombosis will not occur. The range between 22 and 45 seconds (45 seconds is 10 per cent of normal prothrombin activity) is the effective and yet safe range. Bleeding rarely occurs with prothrombin times below 45 seconds; many individuals have elevations in prothrombin time above 45 seconds without experiencing any difficulty; however, hemorrhage will almost invariably occur only in the group which rises above the critical level.

In gauging the dose of dicumarol, the physician should remember that he is estimating the dose for an effect twenty-four to forty-eight hours in the future. After stopping the drug it should likewise be borne in mind that dicumarol may continue to exert an effect for two to seven days.

It should be noted that approximately 15 per cent of patients are significant hyperreactors to dicumarol and will develop excessive elevation of prothrombin time with the usual dosage. This emphasizes the necessity for frequent and reliable prothrombin time determinations.

As regards the dose of heparin, the venous clotting time is maintained between 20 to 40 minutes, the normal range being 5 to 10 minutes. We administer heparin in two principal ways. The first is by continuous infusion of 100 mg. of heparin in 1000 cc. glucose or saline solution at the rate of about 25 drops per minute; the second route is by repeated subcutaneous injection of heparin in doses averaging 30 mg. every three hours. This second route has been employed in the majority of our cases and we have found it especially practicable since the heparin administration can be carried out by the nursing staff and does not demand the attention of the physician. Although some groups believe that control of dosage by venous clotting time determination is not necessary, we believe that the venous clotting time should be estimated at least once and preferably twice a day to insure safety.

Anticoagulant therapy would appear to be indicated in deep venous thrombosis, pulmonary embolism, embolic phenomena of intracardiac origin, prophylactically in individuals with a history of previous thromboembolism, following arterial occlusion and in recalcitrant superficial phlebitis. There are a few situations in which we do not usually employ anticoagulants. We are reluctant to do so when a central nervous system operation has been performed recently, in subacute bacterial endocarditis, except when embolic arterial occlusion has occurred, in hemorrhagic blood dyscrasias, in recent threatened abortion when a viable fetus is desired and in obstetrical cases within six weeks of the estimated date of delivery. Careful consideration should be given to the group of cases in which anticoagulants, although not contraindicated, should be used cautiously. First, are patients with liver disease, for such patients may be deficient in the elaboration of prothrombin; second, renal insufficiency, for it is believed that dicumarol and heparin both are excreted in some form by the renal route; third, patients with an open ulcerating wound, since granulating surfaces certainly tend to bleed more easily than do intact wounds which are completely closed; fourth and fifth, individuals with malnutrition and those who are very old since they are likely to hyper-react to anticoagulants. It is believed that this group may be given anticoagulants if necessary but only with special precautions; individuals in this latter classification have been given anticoagulants at this hospital without untoward results.

DOCTOR: What about the toxic and undesirable side effects produced by the anticoagulants? How should they be handled?

DR. COSGRIFF: Hemorrhage is about the only real toxic manifestation of the anticoagulants. Statistics on the incidence of bleeding during heparin treatment are rather infrequent in the literature; we have experienced it in about 1 per cent of our group. As regards dicumarol, the Mayo Clinic's figures are the most extensive. They encountered mild bleeding in about 2.5 per cent of their dicumarol-treated patients and major hemorrhages in another 2 or 2.5 per cent. In our group mild bleeding was encountered in 2 per cent of those treated with dicumarol.

As to the management of hemorrhage occurring in the course of heparin treatment, the drug is discontinued at once and a transfusion of blood or plasma is given. This does not reduce the clotting time precipitously to normal but does return it toward the safer range. It is reported that administration of protamine sulfate (5 to 10 cc. of a 1 per cent solution) will return a venous clotting time, which has been excessively prolonged by heparin immediately to normal. However, this treatment has not been used by our group.

As regards bleeding occurring with dicumarol, first stop the drug, then administer synthetic vitamin K (menadione bisulfite) in massive dosages of 60 to 75 mg. parenterally. Reports in the literature and our own experience indicate that this dosage of menadione will return an excessively elevated prothrombin time to within the safe range in approximately 85 per cent of the patients within twelve to forty-eight hours following administration. It should be emphasized that there is no certain method for predicting if and how rapidly an individual will react to vitamin K other than by following the prothrombin time carefully at intervals of six to twelve hours until the desired effect is produced.

In bleeding during dicumarol therapy one should aim at obtaining an immediate reduction of prothrombin time. This may be done by the use of whole blood or plasma. We have had the most experience with the administration of 500 cc. of reconstituted lyophilized plasma which reduces the prothrombin time from the excessively elevated dangerous levels to within safe limits immediately after administration. Such a reduction is maintained for approximately six to ten hours, at which time the prothrombin time has returned toward that present before the administration of the plasma. Therefore, when bleeding is taking place plasma should be administered at once in order to obtain an immediate effect and should be repeated several times at proper intervals until prothrombin time determinations indicate that the synthetic vitamin K which was given has permanently returned the prothrombin time to safe limits. The risk of possible serum hepatitis must be considered when the decision to employ plasma is made.

As to the general management of a patient, we believe in *complete* bed rest. This entails lying quietly in bed, no undue active motion, no leg exercises, no massage and no straining on the bed pan and analogous efforts. Dr. Linton at the Massachusetts General Hospital determined the venous pressure in the lower extremity veins in individuals before and during performance of the Valsalva experiment, which is analogous to straining on the bed pan, at which site many people have been known to die from pulmonary emboli. He found that the venous pressure in the lower extremities was raised as much as four times the control level during this effort. It is not difficult to visualize the distention which occurs in the deep veins of the extremities and in the pelvis under such circumstances and the effect that this might have on loosening thrombi from the vein wall.

The foot of the bed is usually elevated to 15 degrees thus encouraging venous return and preventing undue stasis.

If pulmonary embolization has occurred, digitalization has been freely employed for any signs of cardiac failure or acute cor pulmonale. Dr. de Takats has shown in dogs that a pulmonary embolus produces bron-

chospasm, pulmonary artery spasm and changes in cardiac rhythm and coronary flow. The mechanism of such changes may be partly vagal reflexes. These effects were decreased by atropine and papaverine. We believe at the present time that, in patients with large pulmonary emboli, papaverine and atropine may help. We have been employing papaverine, 60 mg. intravenously every four hours, for the first thirty-six hours. Atropine has been given in doses of 1 mg. intravenously or intramuscularly every four hours for this same period.

Oxygen has been employed freely. When severe pleuritic pain has been present and not controlled by the usual measures, intercostal nerve block frequently has been effective in reducing or completely removing that complaint.

Now a word as to the philosophy of the use of anticoagulants in general. Any physician who intends to use anticoagulants should have at his ready disposal proper control of these drugs. The dosage of heparin is properly controlled at the present time by a venous clotting time determination done at least once and preferably twice a day. The effect of dicumarol must be controlled by a prothrombin time determination done daily. We believe that the danger of bleeding in anticoagulant therapy is very real and that careful control and supervision is imperative. If carefully controlled, however, we believe that the *proper* employment of anticoagulants is safe and the most important procedure in the management of thromboembolism.

Dr. Kneeland: Two weeks ago I was participating in a symposium on infectious diseases at a famous university clinic and one of the staff members presented the case record of a patient with pneumococcus meningitis. As he was describing the various clinical phenomena and what was done about them, he said "And of course on the second day of hospital admission we did a bilateral femoral vein ligation. As we all know in a situation like this, where a patient is in bed with a high fever, dehydrated and very ill, he is likely to develop phlebothrombosis and subsequently pulmonary embolism."

That was a rather surprising statement to me because of the casual way in which it was interjected into the case history as part of a routine procedure which everyone naturally would take more or less for granted. It indicated, however, that there is another school of thought on the management of these conditions. I should like to ask Dr. Habif to present his views in regard to vein ligation.

Dr. David V. Habif: As has been pointed out previously, the aim of treatment of thrombosis of the deep veins of the lower extremity is to prevent a fatal or non-fatal embolus; to prevent progression of the disease by limiting its propagation proximally, distally and into the small radicles of the calf; to further more rapid subsidence of the process than occurs with conservative treatment; to shorten convalescence and, in so far as possible, to prevent or lessen the edema, pain, varices and ulcers which occur in the postphlebitic syndrome.

The prophylactic measures which are carried out in the surgical services are many: Sharp dissection with careful hemostasis, avoidance of tight dressings, tight abdominal binders and tight tourniquets on the legs, elevation of the legs with leg and body exercises, frequent turning of the patient, encouragement of deep breathing, the use of CO_2 to aid in deep breathing and in the prevention of atelectasis and pneumonia and early mobilization (which means walking on the first postoperative day). We have come to frown upon allowing a patient out of bed the first postoperative day only to sit in a chair. We believe that the resultant stasis is perhaps worse than having the patient in bed. It has been found that prolonged immobilization will lead to a higher incidence of thromboembolism; in our own clinic, the incidence of thromboembolism in 500 patients treated with the usual ten to fourteen days of postoperative bed rest was 2.4 per cent compared with 1 per cent in 500 patients treated with early mobilization. Others, however, have reported no change in the incidence of phlebothrombosis or

embolus with bed rest as compared with early mobilization.

STUDENT: When in the postoperative period is thrombosis or embolism most apt to occur?

DR. HABIF: Phlebothrombosis commonly manifests itself between the fourth and fourteenth day after operation but may occur as early as the second or third day and any time thereafter.

We are especially interested in the long veins of the leg and the pelvis since we know that emboli arising elsewhere are usually non-fatal. The process is believed to start in the veins of the feet, progress to the calves, then up to the thigh into the iliac veins. The three most common types we see on the surgical service are phlebothrombosis, or thrombophlebitis of the calf, severe iliofemoral thrombophlebitis and pulmonary embolus without an obvious source.

The arguments of the advocates of surgery for ligation of the superficial femoral and the common femoral veins are that the operation is simple, that it can be done under local anesthesia and that the operative mortality is almost zero. The course of the disease is altered in that the pain and the inflammatory process subside more rapidly with removal of the thrombus and convalescence is shortened, the average return to health being reduced to four and one-half days. The patient can be released from the hospital within eight and one-half days. Femoral vein ligation protects from added morbidity and eliminates the chance of a fatal embolus. Phlebitis treated with anticoagulant therapy manifests itself after stopping the anticoagulant therapy and infarcts have been reported to occur after the prolonged use of heparin when the heparin was stopped.

The indications set down for bilateral ligation are the presence of a venous thrombosis in the deep veins of the lower extremity; the occurrence of a non-fatal pulmonary embolus irrespective of whether or not the legs show signs of thrombosis; a concomitant rise in temperature, pulse and respirations postoperatively in a patient in whom these symptoms cannot be explained by some other cause; unilateral thrombosis even though there are no signs in the opposite leg (it is well known that at least 30 per cent of patients with unilateral symptoms will show thromboses in the opposite leg although no symptoms appear there); prophylactically in patients over fifty subject to major surgical procedures, particularly abdominal and pelvic; patients with carcinoma; following hip fractures (especially intertrochanteric) and prostatectomy. The older the patient the more likely a fatal embolus. The operation can be done prior to the major procedure or at the same time.

Now what are the arguments against surgery? It is an operation and it will be done needlessly at times. However, ligation or removal of a segment of the superficial femoral vein of a normal leg ordinarily causes no disturbance. Ligation of the common femoral vein is at times associated with profound shock, the mechanism of which is not clear, and we have had one death in this clinic from ligation of a common femoral vein. The edema of the affected leg often is increased, especially after common femoral vein ligation. Such edema appears early and may be marked but eventually decreases. A high percentage of the ligated group are found to have mild edema one year following the procedure and there is no opportunity to recanalize. However, there is some argument about whether one should recanalize, some groups believing that persistent total blockage of the vein will lead to better collateral circulation.

Five per cent of those who have a bilateral superficial vein ligation have been reported to have subsequent non-fatal pulmonary emboli, necessitating treatment with anticoagulant therapy. The thrombus may appear above the point of ligation as well as progressing distally. Surgery does not take care of the emboli arising in the heart. There is a fear of dislodging the thrombus as the result of introduction of a cannula proximally to the point of incision in the vein. There is an incidence of wound infection slightly less than 2 per cent.

The operation is best done within forty-eight hours of the detection of the thrombosis. The classical case for ligation is the one in which the process is confined below the knees, especially in the calf veins. A vertical incision is made, as recommended by the Boston group, 1 inch above the groin for a total of 3 inches directly over the femoral artery. The lymph nodes, lymphatics and femoral artery are retracted laterally and the saphenous vein medially. A ligature is placed about the common, deep and superficial veins. If the common vein is thrombosed, it is opened. The thrombus is aspirated and the common femoral vein ligated. If the common femoral vein is normal, the superficial vein is opened, aspirated with a rubber catheter or glass cannula up to the bifurcation of the vena cava and then ligated. Bleeding must be free. If you have an older patient with poor collateral circulation and absence of pulses in the feet, ligation of the common femoral with the internal saphenous is not advised. In this clinic we prefer the superficial femoral vein for several reasons. One, we frown upon common femoral vein ligations because of the possibility of shock and death; two, the exposure is more difficult because of the collateral circulation of the common femoral vein. It is short and cannot be divided easily. One enters the lymphatic area and there is occasionally a collection of lymphatic fluid in the wound postoperatively. The superficial femoral vein nearing its junction with the profunda has few tributaries and its exposure is quite easy.

Some surgeons throughout the country have advocated ligation of the iliacs and the inferior vena cava. This requires an abdominal incision and a general anesthetic. The argument for inferior vena cava ligation is that an iliac ligation has to be bilateral; if one has a patient with thrombophlebitis of the iliac veins giving off repeated emboli, with or without a previous femoral vein ligation, vena cava ligation may be justified. At present, we do not agree with the protagonists of inferior vena cava ligation, believing that such a major procedure should be avoided by anticoagulant therapy which adequately obviates any further emboli.

As to axillary and saphenous thromboses, it is well known that the incidence of emboli from these sources is very small. Prior to the use of anticoagulant therapy, we ligated the saphenous vein occasionally.

DOCTOR: What are the principles of management of suppurative thrombophlebitis?

DR. HABIF: Vein ligation proximal to the process is mandatory. Moreover, remember that in the case of pelvic vein involvement, not only is the vena cava ligated but both ovarian or spermatic veins. It is believed that anticoagulant therapy may be of value following ligation; however, our group has had no experience with this problem.

On the surgical service "leg rounds" have now become routine, like "sleeping pill rounds" and "carthartic pill rounds." One must appreciate the high incidence of thrombi producing no clinical symptoms whatever and that at least 50 per cent of older people harbor small segments of thrombi in the veins of the feet, legs and calves. It is important not to overlook a deep vein thrombosis in the presence of an obvious internal or external saphenous vein phlebitis.

If an adequate organization for the control of anticoagulant therapy is not available and the patient is in the hospital, then we think ligation is indicated. At present, we do not believe that ligation is the answer to the problem and until a simple, effective prophylactic means is found anticoagulant therapy seems more rational and gives excellent results.

Before closing this discussion of surgical indications in thromboembolism I should like to say something about lumbar sympathetic block. Any vascular occlusion will produce vasospasm in the collateral vascular bed and in adjoining major vessels when they are in the same vascular sheath. Pain and edema are due in part to vasoconstriction. The degree of vasospasm seems to be proportional to the perivascular involvement and the exudate around an acute thrombophlebitis. There is pain, a sense of

constriction. The limb is cold, slightly blue, with diminished or absent arterial pulsations. To combat this situation, lumbar block was first advocated by Leriche and Cournand and popularized by Ochsner and DeBakey. The procedure involves blocking the first, second, third and fourth lumbar ganglia with 1 per cent procaine. It does relieve the pain, most often dramatically, although this may be transitory and the block must be repeated once or twice again. It relieves the vasospasm, allowing for compensatory venous circulation of the affected limb, and it relieves the edema. It restores the arterial pulsations and, in the majority of cases, the process subsides rapidly. A severe degree of vasospasm is usually seen, however, only in the extreme cases of acute thrombophlebitis and we have had few cases requiring lumbar block.

SUMMARY

DR. FREDERICK K. HEATH: The common denominator, prerequisite to an understanding of the mechanisms upon which present day therapy of thromboembolism is based, is the increased tendency of the blood to clot. This may be demonstrated by the Lee-White method of determining the clotting time by which, if lucite or paraffin coated tubes are used, an actual decrease in coagulation time below the normal may be noted. Why the blood tends to clot faster is not known but poor muscle tone, venous stasis and tissue damage seem to be predisposing factors.

At any rate, clotting occurs and a thrombus is formed. In about 90 per cent of instances, this develops below the inguinal ligaments, most frequently in the deep veins of the calf. Early in its evolution no signs or symptoms are found. As the clot grows, inflammation of the vein wall, representing the reparative phase, may result in tenderness; obstruction of the vein may produce mild edema of the tissue drained. With growth of the 'tail' to involve larger veins, more venous obstruction and more edema may result until, with adherence of the 'tail,' definite venous obstruction is present and swelling of the calf ensues. At this juncture a considerable inflammatory reaction is present producing the common findings of pain, tenderness, fever, leukocytosis and elevation of the sedimentation rate. When these are marked, vasospasm may also occur. The typical picture is now one of acute thrombophlebitis as described by Ochsner. When the inflammatory process is less severe, or perhaps earlier in the course, the pattern resembles phlebothrombosis. Whether more profound differences exist between these clinical entities is not yet clear.

The rate of healing is variable but takes place first by adherence of the clot and its 'tail,' which occurs about the fifth day, and then by endothelialization, completed by the tenth to twelfth day if growth can be prevented. These time factors are important not only because upon them is based the duration of anticoagulant therapy but also because they suggest when ligation is most needed.

The breaking-off of the thrombus or its 'tail' before these are adherent, with consequent pulmonary embolization, is a major event in the pathologic sequence and may produce a dramatic clinical picture. Again this aspect is variable, ranging from small emboli producing mild pleuritic pain with no signs to massive embolization causing sudden death. Between these extremes, deep constant pain, cyanosis, reflex dyspnea, cough and hemoptysis (rather infrequently), râles and, occasionally, pleural effusion may be encountered. Serious impairment of the pulmonary arterial flow and an accentuated pulmonic second sound may herald right heart failure and electrocardiographic evidence of acute cor pulmonale; nor should the presence of abdominal findings of pain and muscular spasm fail to suggest the possibility of a basal infarct with diaphragmatic irritation. The appearance of signs or symptoms referable to the lungs or pleura should always call to mind the possibility of thromboembolism.

The aim of anticoagulant therapy is to prolong blood coagulation so as to prevent further growth of the thrombus in the vein of

origin. If this can be done, the thrombus will become adherent and repair may take place before the 'tail' breaks off to become an embolus. When embolization has already occurred, the aim is not only to attain the same end at the original site so as to prevent further potential embolus formation but also to prevent proximal propagation of the thrombus which forms behind the embolus lodged in the lungs. This is carried out by the use of heparin and dicumarol with daily careful clotting and prothrombin time determinations. Statistics indicate that the results of anticoagulant therapy are excellent both in achieving a favorable local result as well as in preventing pulmonary embolization or its recurrence. Fatal pulmonary embolization, subsequent pulmonary embolization and venous thrombosis have each been reduced to about 1 per cent. Hemorrhage has been the only serious toxic manifestation of anticoagulant therapy. It is infrequent with adequate control and can be successfully combatted by the use of plasma and blood, and by vitamin K when dicumarol is the anticoagulant.

Contraindications to anticoagulants exist: subacute bacterial endocarditis, hemorrhagic blood dyscrasias, recent threatened abortion, obstetrical cases near term and after a recent central nervous system operation. Anticoagulants obviously cannot be used prophylactically in the immediate preoperative period. They should be used with caution in liver disease or renal insufficiency and in patients with ulceration or malnutrition and in very old patients.

At the present time, bilateral ligation of the femoral vein distal to the point of entry of the deep femoral vein is the surgical approach of choice. No obvious advantages can be expected from this mode of therapy which make it superior to anticoagulants. It is therefore usually reserved for situations in which anticoagulant therapy cannot be used.

Clinico-pathologic Conference

Cardiac Disease with Cardiac Insufficiency and Peripheral Vascular Complications*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. A., a forty-two year-old married Negro truck driver, entered the Barnes Hospital on May 15, 1946, complaining of shortness of breath and swelling of the abdomen and lower extremities. The family history was not known; in regard to the past history, the patient maintained that he had been in good health all of his life but his wife stated that he had had one attack of rheumatic fever and had a "leaky heart" for some years. Otherwise, no significant illness was known and the systemic history was essentially negative. The patient had been married four times. For years he had worked as a laborer, truck driver or at other jobs which entailed strenuous exertion. He neither drank nor smoked.

In 1941, the patient applied for a defense job; he was told that he had a "bad heart" and was rejected. He had no cardiac symptoms, however, until the spring of 1945, when he first noticed shortness of breath on exertion which was soon followed by an intermittent non-productive cough. Three or four months later, he had his first attack of severe shortness of breath at night, subsequently, paroxysmal nocturnal dyspnea recurred with increasing frequency. Shortly after the first attack, swelling of the ankles was noted, particularly in the evening, and the patient was advised by his physician to take two weeks rest in the hospital. He disregarded the advice and continued to work. All of his symptoms increased in the next two months and ankle edema became persistent. He was given digitalis and mercupurin and the swelling of the legs and shortness of breath decreased.

Five months prior to admission, he was told for the first time that his blood pressure was elevated; his physician stated that the reading was "220"; the patient continued to take digitalis daily and he received injections of mercupurin every two or three days. Despite these measures, the swelling of the lower extremities gradually progressed and his abdomen began to swell; concomitantly, there was marked diminution in urinary output. In the month before entry, the patient continued to work but his symptoms increased rapidly during this period.

At the time of admission, the physical examination revealed the temperature to be 37.7°C., pulse 120, respirations 20 and blood pressure 194/155. The patient was a well developed colored male who was in acute respiratory distress. His skin was cold and moist and the nail beds were cyanotic. The pupils were small and reacted normally to accommodation but not to light; the sclerae and conjunctivae were clear. Examination of the fundi revealed the arterioles to be very narrow and tortuous; a few exudates were seen but no hemorrhages were present. No abnormalities were noted in the upper respiratory tract. On percussion of the chest, there was dullness at both lung bases

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posteriorly; over these areas, tactile fremitus was decreased and medium moist râles were audible. Breath sounds were of good quality throughout. Cardiac dullness extended 16 cm. to the left of the midsternal line in the fifth interspace and 7 cm. to the right in the fourth interspace. A grade II systolic murmur was heard over the apex and a protodiastolic gallop rhythm was audible over the entire precordium. The abdomen was distended and signs of ascites were prominent. The liver dullness was percussed 4 cm. below the right costal margin but the edge was only questionably palpable. Four plus edema extended up to the iliac crests and involved both the penis and scrotum. The neurologic examination was within normal limits.

The laboratory findings were as follows: Blood count: red cells, 6,420,000; hemoglobin, 17 Gm.; white cells, 10,650; differential count: eosinophiles, 1 per cent; stab forms, 5 per cent; segmented forms, 68 per cent; lymphocytes, 21 per cent; monocytes, 5 per cent. Urinalysis: albumin, 3+; sediment, negative. Stool: guaiac, negative. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 33 mg. per cent; total blood protein, 6.2 Gm. per cent; albumin, 3.2 Gm. per cent; globulin, 3.0 Gm. per cent. Venous pressure: 255 mm. NaCl. Circulation time (decholin): 45 seconds. Corrected sedimentation rate: 0.3 mm. per minute. Electrocardiogram: Low voltage in leads II and III; S-T segments depressed in leads I and II; Q wave in lead C-F IV; left axis deviation. Roentgenogram of the chest: "There is second degree cardiac enlargement and fluid is present in both pleural cavities."

On entry, the patient was placed in an oxygen tent and given morphine, aminophylline and digitalis. His general condition improved somewhat but, due to the marked edema of the penis, he was unable to void. Twenty-four hours after admission, he was catheterized and subsequently there were no urinary difficulties. Digitalis had very little effect on the pulse rate and oral ammonium chloride combined with intravenous mercupurin were used as diuretics with only moderate effect. From the outset, the patient had a low grade, spiking temperature. The fever was believed to be due to a urinary infection for beta-hemolytic streptococci were cultured from the urine repeatedly; although no white cells were noted in any of the urine specimens examined, penicillin therapy was instituted.

On the fifth hospital day, the patient's respiratory difficulty had improved sufficiently to warrant his being taken out of the oxygen tent. He continued, however, to have orthopnea, edema and ascites; likewise, tachycardia and the gallop rhythm persisted. One week after entry, he had an episode of substernal pain of mild to moderate severity which was relieved by nitroglycerine and aminophylline. Two days later he complained of pain, numbness and tingling of both feet and was given papaverine intravenously. One hour later, he was found in a state of apparent peripheral vascular collapse with Cheyne-Stokes respirations; he was revived by adrenalin and coramine given intravenously. The following day, he developed pain in the right leg and tenderness over the right calf was elicited. The temperature, which had ranged between 37° and 38°C., rose to levels between 38° and 39°C. for several days. The right foot became cold and gangrenous and discoloration of the skin extended up to the mid-thigh. A paravertebral sympathetic block with novocaine was performed and heparin and dicumarol therapy were begun. Neither favorably influenced the course of the gangrene. Repeat electrocardiograms showed no essential change from the record obtained on admission. The icteric index rose to 20 units but fell to normal within a few days. Repeat urinalyses were all normal except for the appearance of an occasional cast. The non-protein nitrogen at the time of development of gangrene rose to 50 mg. per cent but it, too, fell rapidly to normal. The white blood count was 20,000 and the sedimentation rate rose to 1.2 mm. per minute. Dicumarol therapy lowered the prothrombin time to 33 per cent of normal.

The patient developed a generalized erythematous scaling skin eruption thought to be due to penicillin sensitivy; he was given benadryl and penicillin was withdrawn. He continued to do poorly; the tachycardia and gallop rhythm persisted. The signs of fluid at the right lung base increased as the patient became disoriented and his respirations gradually grew more labored. On the day before his death, his temperature rose to 40.3°C. and the following day pain in the right leg, which had subsided somewhat, again became severe. The patient expired quietly on June 8, 1946.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presents us with the opportunity of discussing certain phases of cardiac failure and its complications. It would seem important that we first attempt to establish the etiology of the heart disease which this patient certainly had. The history in this regard is rather confusing. The patient's wife stated that he had rheumatic fever at one time and a "leaky heart" for years. The patient, on the other hand, stated that he first became aware of cardiac disease five years before entry; at that time, when he was thirty-seven years of age, he was rejected when he applied for a defense job because of a "bad heart." Dr. Massie, from the evidence at hand, what is your opinion as to the type of heart disease with which this patient was afflicted?

DR. EDWARD MASSIE: I would say unhesitatingly that he had hypertensive cardiovascular disease.

DR. ALEXANDER: Do you believe that when the pathologist presents his findings he will describe a lesion of the mitral valve?

DR. MASSIE: No, I do not.

DR. ALEXANDER: Dr. Smith, what is your opinion?

DR. JOHN R. SMITH: I agree with Dr. Massie that this patient did not have rheumatic heart disease. I would add however to the diagnosis of hypertensive cardiovascular disease that of coronary artery disease.

DR. ALEXANDER: Seemingly, the patient had some evidence of heart disease at the age of thirty-seven when he was rejected for a defense job. Despite this fact, he continued to work until a month or so before entry to the hospital. Is such a history compatible with rheumatic heart disease?

DR. MASSIE: If he had had rheumatic heart disease with minimal mitral insufficiency, he could have led a perfectly normal life. The murmur was described as grade II and apparently was not very intense; such a finding is compatible with mitral insufficiency of only moderate degree. We are handicapped in our interpretation by the fact that, although we are told that five years before entry the patient had a "bad heart," we know nothing of his blood pressure until five months or so before he died.

DR. ALEXANDER: It seems remarkable that he was able to do heavy physical labor almost up to the time he came into the hospital. If the etiology of the heart disease were rheumatic, would it have been likely that the patient could have worked as long as he did?

DR. MASSIE? If he had had mitral stenosis, I would agree that it is unlikely that he could have gotten along so well for so long a period; on the other hand, I still believe that the history is compatible with moderate mitral insufficiency and no stenosis.

DR. ALEXANDER: What about the episodes of paroxysmal nocturnal dyspnea? Are these of importance in differential diagnosis?

DR. MASSIE: To some extent they are; paroxysmal nocturnal dyspnea is more frequently seen in association with hypertensive cardiovascular disease than with rheumatic disease.

DR. ALEXANDER: Is there agreement with the views expressed by Drs. Massie and Smith; namely, that the pathologist will report cardiac enlargement, hypertrophy and perhaps involvement of the coronary vessels but no rheumatic valvulitis?

DR. W. BARRY WOOD, JR.: I do not see how such a view can be accepted if one considers the past history. How can hypertensive cardiovascular disease explain a "leaking heart" for many years? How can

coronary artery disease do so? Although there is considerable evidence for both of these diagnoses, they will not explain the past history *in toto*. One either has to disregard the past history or else one has to postulate a lesion or lesions which would cause such physical signs.

DR. WILLIAM H. OLMSTED: How reliable is the past history?

DR. ROBERT J. GLASER: I can say that those of us who spoke to the patient's wife believed that she was a very intelligent woman and a good observer. The patient was, of course, critically ill when he was admitted and the history which he gave may well be open to question; we were all quite convinced, however, that his wife was a dependable informant.

DR. EDWARD H. REINHARD: Is it not possible that this patient had other murmurs prior to his terminal episode which disappeared with the onset of severe decompensation?

DR. MASSIE: If the patient had been fibrillating, I could understand the absence of a diastolic rumble, particularly of the presystolic phase; likewise, if auscultation was not repeated frequently, such a murmur might not have been heard but this patient had a regular rhythm and I am sure that he was subjected to repeated careful cardiac examination. Therefore, I would hesitate to believe that the murmur was missed.

DR. ALEXANDER: The heart was quite huge, was it not? It was described as being enlarged to both the right and left. Would such enlargement commonly occur in pure hypertensive cardiovascular disease? It is recorded that the systolic blood pressure was only 194 mm. of Hg.; of course, that reading was taken during marked failure and an earlier reading was said to have been 220 mm. of Hg. Would the presence of rheumatic valvular involvement better explain the size of the heart or does not this point disturb you in your interpretation?

DR. MASSIE: I do not think that rheumatic involvement need be postulated to explain the heart size; I believe it is compatible with hypertensive cardiovascular disease in its more advanced phase and in this case the process was indeed advanced.

DR. ALEXANDER: Dr. Bottom, did the cardiac x-ray findings suggest mitral heart disease to you?

DR. DONALD S. BOTTOM: No. The aorta was somewhat prominent and seemed more consistent with a diagnosis of hypertensive cardiovascular disease. When a heart is so markedly enlarged and cardiac failure has ensued, it is impossible to make a definitive x-ray diagnosis. We cannot rule out mitral disease in this particular case.

DR. VIRGIL C. SCOTT: I would appreciate Dr. Bottom's explaining what the radiologist means by the term, "second degree cardiac enlargement."

DR. BOTTOM: There are three degrees of cardiac enlargement according to the radiologist's classification: second degree enlargement indicates that the left cardiac border extends to the mid-portion of the left lung and that the enlargement to the right is such that the entire cardiac shadow takes up about 70 per cent of the total intrathoracic diameter. In third degree enlargement, the left border extends to the chest wall at the inner margin of the ribs and right sided enlargement is also marked.

DR. ALEXANDER: All of us, I think, will agree that the patient had hypertensive cardiovascular disease; we still have not settled the question as to whether, in addition, he had rheumatic heart disease. Is there anything else, Dr. Wood, beside the history which you would like to emphasize in this connection?

DR. WOOD: No, except to mention the point that Dr. Levine in Boston has frequently made, namely, that patients who have mitral disease and subsequently develop hypertension often do well. I do not know if the cardiologists here accept Dr. Levine's views in this regard.

DR. MASSIE: If the hypertension is moderate, I agree that it may favorably effect the patient's course.

DR. SCOTT: I would like to ask Dr. Massie about the polycythemia recorded in this case. Usually in cardiac failure, pa-

tients have hemodilution and the red count and hemoglobin are relatively low.

DR. MASSIE: I would like to refer Dr. Scott's question to Dr. Carl Moore.

DR. CARL V. MOORE: The red blood cell count recorded here could be a perfectly normal one for a robust male but there is one other possibility which would explain the elevated red blood cell count. This man was cyanotic on admission. If the cyanosis had been present for a matter of ten days or two weeks, he could have developed relative polycythemia in spite of the fact that he was in cardiac failure.

DR. ALEXANDER: Let us now go on to the apparent arterial occlusion. Was it a thrombus or an embolus?

DR. HENRY A. SCHROEDER: I think it was most likely an embolus, probably arising from a mural thrombus in the heart. The only flaw in such an explanation lies in the fact that the electrocardiograms did not exhibit the characteristic changes of coronary occlusion.

DR. ALEXANDER: Dr. Smith, what cardiac abnormalities are apt to give rise to arterial emboli?

DR. SMITH: Three are usually mentioned: First, subacute bacterial endocarditis; second, mural thrombi secondary to a myocardial infarction which involves the endocardium and third, mural thrombi which arise in the presence of auricular fibrillation.

DR. ALEXANDER: What is the order of frequency of the three?

DR. SMITH: I would think of myocardial infarction first, then of auricular fibrillation and lastly, subacute bacterial endocarditis; none of these is uncommon and the history and physical findings often cast considerable light as to which is responsible for a given arterial occlusion.

DR. ALEXANDER: It was my impression that arterial emboli occur most commonly as a complication of auricular fibrillation.

DR. MASSIE: I think that Dr. Smith was considering the older age group. If one were to consider a group of patients under forty, auricular fibrillation would be associated with mural thrombi and arterial emboli more frequently than would myocardial infarction; on the other hand, in a group of patients above forty the converse would be true.

DR. ALEXANDER: Thank you, Dr. Massie, for clarifying this point. In the case now under discussion, the history states that two days before the patient developed numbness and tingling in his feet he had substernal pain relieved by nitroglycerine. If the substernal pain actually represented a myocardial infarction, is forty-eight hours a sufficient interval for the formation of a mural thrombus?

DR. SMITH: I believe it is rather short.

DR. ALEXANDER: How long a time would you expect to be necessary for the formation of a thrombus?

DR. SMITH: Usually, mural thrombi develop a week or so after the infarction occurs.

DR. ALEXANDER: Would you consider the possibility that a soft clot may have formed within forty-eight hours of an infarct?

DR. SMITH: I think it more likely that the patient had an old myocardial infarct with a mural thrombus which became detached.

DR. ALEXANDER: This man had definite vascular stasis; his venous pressure was very high and his circulation time was prolonged. Would you care to entertain the possibility that the arterial occlusion was due to a thrombus rather than to an embolus?

DR. SMITH: I think not.

DR. ALEXANDER: Here, except for the fact that the time interval seems short, the case for a myocardial infarction with formation of a mural thrombus and subsequent arterial embolization seems strong. The sedimentation rate began to rise three or four days after the episode of chest pain and one or two days after the temperature had risen above its previous level. Would you comment on the importance of these changes, Dr. Moore?

DR. C. V. MOORE: In the majority of patients with myocardial infarction, there is a temperature elevation commonly within twenty-four to forty-eight hours and very

shortly thereafter the sedimentation rate likewise rises. In this case, the lag between the infarction and the rise in sedimentation rate is somewhat longer than is usually encountered.

DR. MASSIE: Dr. Moore's statement concerning the rise in sedimentation rate within forty-eight to seventy-two hours of a myocardial infarction holds in most cases, I think, but it is important to point out that in occasional instances the sedimentation rate after massive infarctions may increase only after quite a considerable period has elapsed; we have seen the rise come as long as ten to fourteen days after the acute episode.

DR. ALEXANDER: It seems that there is little doubt that this patient had a myocardial infarction and a subsequent arterial embolus. Where do you think the peripheral occlusion was, Dr. Schroeder?

DR. SCHROEDER: Probably at the origin of the femoral artery.

DR. ALEXANDER: This man first had bilateral parathesias and later unilateral pain, Dr. Schroeder. Would you comment on the pain and also discuss the usual site of an embolus? Also, what is the status of embolectomy?

DR. SCHROEDER: First of all, there is usually considerable spasm associated with arterial occlusion and it is believed that the pain is at least, to a large extent, associated with the spasm. The embolus is usually located at the bifurcation of the artery for that is where the vessel narrows. If embolectomy is contemplated, it must be done without delay for not only may irreversible changes occur in the tissues supplied by the occluded vessel but also extensive thrombosis of the artery, distal to the embolus, may develop.

DR. ALEXANDER: May spasm *per se* be injurious?

DR. SCHROEDER: Spasm may contribute to decreased collateral circulation which affords the only source of blood supply to the limb distal to the embolus.

DR. ALBERT ROOS: I should like to suggest that thrombophlebitis of the femoral vein rather than arterial embolism may have occurred in this patient. I remember a case in which, at post mortem examination, only thrombophlebitis of the femoral vein was demonstrated but which clinically had presented the typical manifestations of femoral arterial obstruction.

DR. ALEXANDER: Your point is well taken; we recently discussed the question of arterial spasm secondary to venous stasis at one of these conferences. Dr. Edgar Allen has pointed out that ischemia and necrosis of the vessel wall may follow as a result of stasis; therefore, prompt treatment is doubly important. Dr. Smith, would you have advised embolectomy in this case?

DR. SMITH: I would have considered it but the lesion was difficult to localize and I thus would have been doubtful about advising it.

DR. ALEXANDER: How may the site of an embolus be localized?

DR. SMITH: The presence or absence of arterial pulsations at a given level, the distribution of pain and the line of demarcation of ischemia all must be considered in establishing the locale of an embolus. The histamine wheal test may also be helpful. Often, accurate localization is impossible.

DR. ROOS: Embolectomy is particularly difficult if the embolus lies in an artery above the inguinal ligament.

DR. ALEXANDER: This patient was given anticoagulants, heparin and dicumarol. Dr. Moore, what is the effect of these agents?

DR. C. V. MOORE: They are used to prevent further intravascular clot formation. They, of course, have no effect on the clot already formed except to prevent its further propagation.

DR. ALEXANDER: The prothrombin time fell to 33 per cent of normal. Is that the desired range?

DR. C. V. MOORE: We do not have well defined standards for comparison because we have been using a different method for prothrombin times from that which the Mayo Clinic has employed. We attempt to keep the prothrombin time between 10 and

30 per cent of normal so the value of 33 per cent would probably be satisfactory. I am not sure, however, how well figures from various clinics can be correlated. With our method, a prothrombin time of 10 to 30 per cent does represent marked hypoprothrombinemia.

DR. ALEXANDER: Would you comment on the danger entailed when the prothrombin time falls to low levels?

DR. C. V. MOORE: The occurrence of serious hemorrhage must be kept in mind.

DR. ALEXANDER: Does the coagulation time vary directly with the bleeding time?

DR. C. V. MOORE: No, nor does it vary too directly with the prothrombin time either. When the prothrombin time is low, one cannot be sure whether the coagulation time is prolonged; nevertheless, in spite of this fact, it is true that some patients who have low prothrombin times with normal coagulation and bleeding times do have serious hemorrhage. The exact explanation for this phenomenon is not clear.

DR. ALEXANDER: In instituting anticoagulant therapy, what is the method of choice?

DR. C. V. MOORE: This patient received what we consider the optimum regimen. Heparin was administered to cause immediate prolongation of the coagulation time and concomitantly dicumarol was given; an interval of twenty-four to forty-eight hours is usually necessary before the prothrombin time falls to adequate therapeutic levels and then heparin is discontinued.

DR. ALEXANDER: How is heparin best administered?

DR. C. V. MOORE: Probably the best method of giving heparin is by continuous intravenous infusion in 5 per cent glucose in water; our usual plan is to adjust the infusion so that 25 to 30 mg. of heparin are introduced every hour; coagulation times are checked hourly by the capillary tube method. In our experience, this plan has been quite satisfactory.

DR. ALEXANDER: In summary, the discussion in this case has covered various aspects of this man's illness which lay in his cardiovascular system. It is believed that he most likely had hypertensive cardiovascular disease and coronary artery sclerosis, probably with myocardial infarction. Subsequently, it seems likely that a mural thrombus formed in the left side of the heart, became detached and led to occlusion of the right femoral artery. Profound cardiac insufficiency complicated the clinical problem. Questions have been raised as to the possibility that rheumatic valvulitis was a major factor in the cardiac disease and thrombophlebitis has been mentioned as a possible cause of the peripheral vascular phenomena.

Clinical Diagnosis: Hypertensive cardiovascular disease; cardiac insufficiency; coronary artery sclerosis; myocardial infarction; mural thrombus and femoral artery embolism.

PATHOLOGIC DISCUSSION

DR. RICHARD D. JOHNSON: The significant gross findings were in the serous cavities, heart and in the lower extremities. The peritoneal cavity contained 1,000 cc. of yellow, clear fluid. There were 550 cc. of similar fluid in the right thorax, 100 cc. in the left thorax and 200 cc. in the pericardium.

The heart weighed 675 Gm. and all chambers were dilated. The left ventricle measured 15 mm. in thickness, the right 8 mm. The anterior descending branch of the left coronary artery was totally occluded by a grey thrombus. In the anterior wall of the left ventricle, extending from the apex to within 5.0 cm. of the base and involving the anterior portion of the interventricular septum, was an area of yellow and red, mottled, soft tissue in which no muscle bundles could be identified. Its cut surface retracted slightly. Attached to the overlying endocardium was a grey and brown friable thrombus.

Both lower extremities showed blue-black discoloration of the distal portions with clearcut lines of demarcation 12 to 14 cm. above the external malleoli. The discoloration was more intense in the right extremity with black shrivelled toes. There was a grey and red thrombus occluding the right pop-

liteal artery and a red thrombus filling and distending the right femoral and iliac arteries. The arteries of the left leg were patent. No thrombi could be demonstrated in the major veins.

The kidneys weighed 200 and 180 Gm. respectively; their cortical surfaces were finely granular without significant reduction in the width of the cortex.

DR. ROBERT A. MOORE: On the basis of the gross findings, I think that we can answer the first question that Dr. Alexander proposed in regard to the nature of the heart disease. There was no evidence of rheumatic heart disease; furthermore, there was no abnormality of the aortic valve so that we may conclude that the patient did not have syphilitic heart disease. To the pathologist, there was definite inferential indication of hypertension as evidenced by cardiac enlargement without other evidence of heart disease and by the changes observed in the kidneys. There was sclerosis of the coronary arteries and other arteries of slight to moderate degree and complete occlusion of the left descending coronary artery. I assume from the discussion, Dr. Alexander, that one of the major points of interest to the clinicians is the time relation of the occurrence of the various lesions which were mentioned in the gross description. Let us turn to the microscopic slides in order to attempt to correlate the clinical features in this case. Figure 1 represents a section of the left descending coronary artery and one of its branches. The muscle wall is thin in some areas and the lumen is occupied by a mass which Dr. Johnson described as gray, firm and adherent and which retracted from the cut surface as a completely organized thrombus. Whatever thrombus was there was completely replaced by fibrous tissue through which recanalized channels pass. Thus, in the heart, 3 cm. from the origin of the left descending coronary artery, there is a completely organized lesion which is at least several months old. How much older than that cannot be determined anatomically for, as I have said here on other occasions, the anatomic or histologic age of lesions cannot be determined past the time required for complete healing; there is no change thereafter. Let us next look at a section of the left ventricular wall in the region described by Dr. Johnson as being mottled, red and yellow with a thrombus lying over it. In Figure 2, a typical section is seen showing viable muscle at one point, collapsed muscle at another and necrotic muscle in a third area; in the latter region, the individual muscle fibers have lost their nuclei and their striations. Their cytoplasm consists of homogenous or granular débris. Some of the muscle fibers have completely disappeared. We may therefore assume that the lesion had been present for a sufficient length of time that some of the dead muscle had been removed. That interval would be between three and seven days. Let us look at another region of the myocardium. (Fig. 3.) Here a different picture is seen. The dead muscle has been completely removed and there is nothing left but the outline of the fibrous tissue in between; note particularly that each one of the capillaries is visible. I think that a lesion of this type demonstrates more strikingly than any other means, except by the use of an injection mass, the rich capillary supply to the heart muscle. If one counts the number of capillaries and the number of muscle fibers in an injected preparation, as has been done, it is found that there are more capillaries than there are muscle fibers. In a section such as this when the muscle fibers have disappeared, the capillaries stand out in an extremely prominent fashion. Manifestly, from what I have said about the previous section this lesion is older for here all of the dead muscle has been removed. Thus, we may say that in the same general area of the myocardium, there is a lesion that is several weeks old, I would say from one to three weeks. Dr. Johnson described a thrombus on the endocardial surface of the ventricle in this region. Let us examine that area. In Figure 4, one sees muscle and probable Purkinje fibers which can be recognized by the extremely large and prominent myofibrillae; also, the ap-

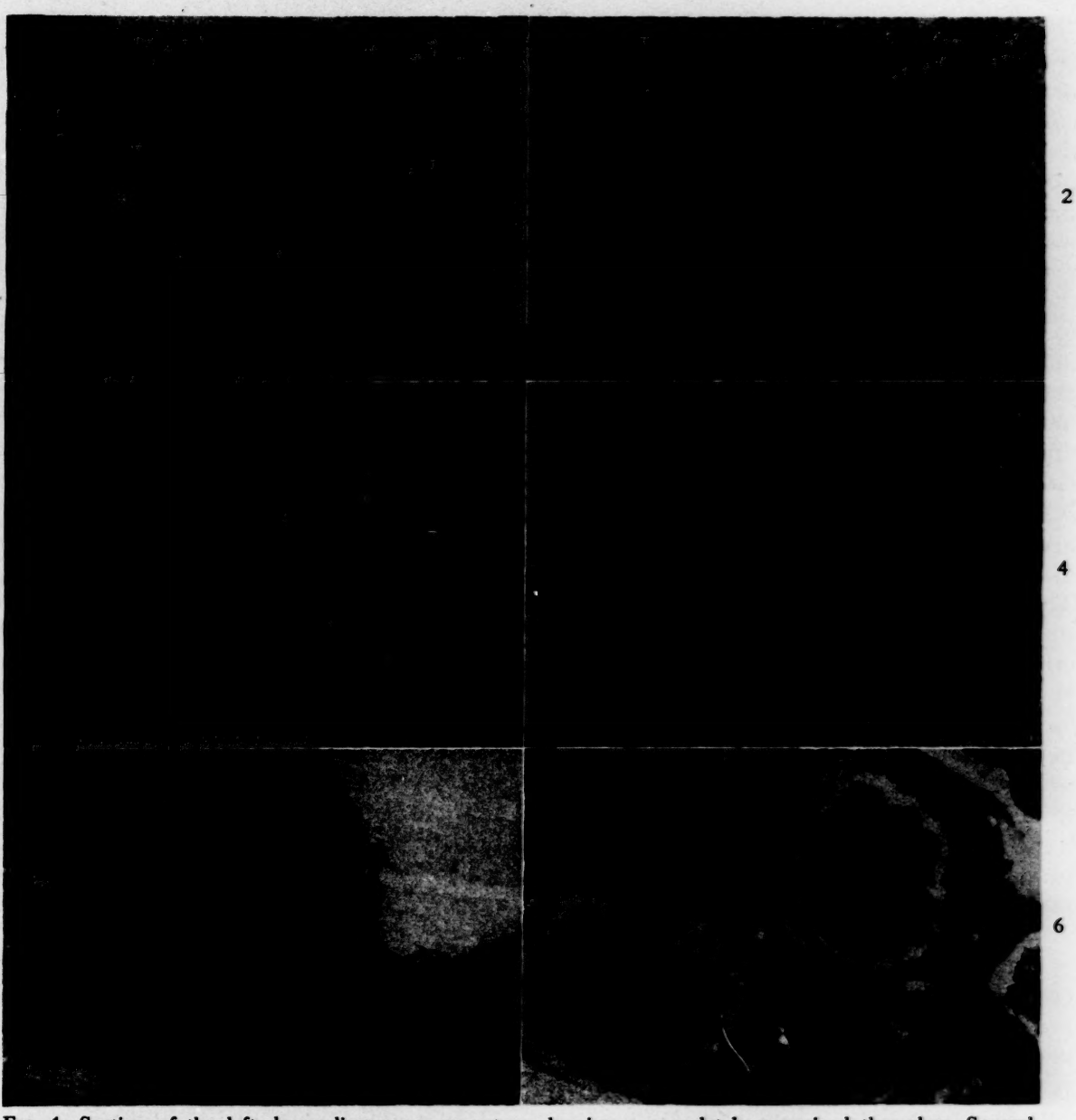

FIG. 1. Section of the left descending coronary artery showing a completely organized thrombus. Several recanalized channels may be seen.
FIG. 2. Section of the left ventricular wall through the area of infarction. Note the area of necrotic muscle.
FIG. 3. Another area of myocardium through an area of older infarction. Note particularly the great number of capillaries.
FIG. 4. Section showing myocardium at the site of thrombus formation.
FIG. 5. Sections through the popliteal artery at the site of the embolus. Organization of the embolus is under way.
FIG. 6. Section of the kidney showing the changes of arteriolar nephrosclerosis.

parent vacuolation of the cells which actually represents the rich store of glycogen in the Purkinje fibers stands out in contrast to the contractile fibers of the heart. The thrombus is seen to be undergoing organization; there are capillary vessels extending out for a short distance and there is also fibroblastic proliferation. The thrombus, in all probability, has been present for a period of several weeks, again probably one to three weeks. The rate of organization depends on so many different factors that I allow myself a good deal of leeway in estimating the age of the individual lesion.

In a section through the popliteal artery (Fig. 5), the internal elastic lamina, the muscular wall, the intima and the embolus contained in the lumen are all visible. At the junction of the intima and the thrombus, fibroblastic proliferation has begun; that is, the organization of the embolus is under way. I would estimate, on the basis of the very minimal degree of organization, that the embolus had occluded the lumen four to eight days before. In the femoral and iliac arteries, thrombus formation, secondary to the embolus in the popliteal artery, had occurred but there was no evidence of organization. That thrombus, therefore, had an age of one to three days.

Let us now consider the other lesions. In a characteristic section of the kidney (Fig. 6) several afferent arterioles can be seen. The glomerular vessels are tremendously thickened and their lumens are greatly decreased in thickness. There is, however, no necrosis in the walls. These sections, therefore, are an example of benign arteriolar nephrosclerosis rather than of malignant nephrosclerosis. The glomeruli show slight thickening of the basement membranes in some instances. Sections of the lungs showed numerous large macrophages containing abundant hemosiderin pigment in the alveoli, evidence of chronic passive congestion.

Now to return to a consideration of the case as a whole assuming that our estimates regarding the age of the various lesions are correct. As I have pointed out, they are reasonably correct as first approximations but, of course, there is much variation in the response of tissues in different individuals to injury or other pathologic changes. It seems likely to me that this patient suffered from hypertension for some time and this process led to the cardiac hypertrophy. During the discussion with Dr. Bottom regarding the cardiac size I asked him if he would estimate the weight of the heart; he gave me the figure of 700 Gm. which certainly compares favorably with the actual weight of 675 Gm. I have seen Dr. Bottom estimate the size of hearts in radiographs frequently and he usually is just as reliable as our scales. Concomitant with hypertension, the patient had a moderate degree of sclerosis of the coronary arteries. Several months ago, one of the coronary arteries, the left anterior descending branch, was completely occluded but sufficient collateral circulation was present to prevent any immediate severe embarrassment and no infarct developed. Several weeks ago, for some reason not now apparent, small foci of infarction started to appear in the heart muscle. In association with the first infarct, a thrombus formed in the left ventricle and four to eight days before the patient's death a piece of that thrombus broke off and lodged in the popliteal artery to give rise to the terminal events.

Anatomic Diagnoses: Arteriosclerosis of the coronary arteries, slight; organized thrombus occluding the anterior descending branch of the left coronary artery; partially healed and recent infarcts of the anterior wall of the left ventricle and apex of the interventricular septum; mural thrombus in the left ventricle; partially organized thrombus in the right popliteal artery with partial occlusion; gangrene of the right ankle and foot and discoloration of the left ankle and foot; arteriolar nephrosclerosis; hypertrophy and dilatation of the heart (675 Gm.); congestion and edema of the lungs, advanced; chronic passive congestion of the liver, spleen and kidneys; hydropericardium (200 cc.); hydrothorax (left, 100 cc.; right, 550 cc.); ascites (1,000 cc.) and edema of the thoracic and abdominal walls, scrotum and the right lower extremity.

Book Reviews

The Essentials of Endocrinology. By Arthur Grollman. Second edition, 644 pp; 132 figures. Philadelphia, 1947. J. B. Lippincott Co. *Price* $10.00.

Dr. Grollman has written a very lucid, clear and simple textbook. The disorders of the endocrine glands are discussed from the physiologic and clinical standpoints in straightforward language and with well chosen material. One does not require a large background of experience in this difficult field in order to understand the presentation. The illustrations are good; the clinical descriptions are adequate. One adverse criticism might be that there is a tendency to present a group of symptoms rather than to bring out their appearance in the course of a given disease.

The material of each chapter is accurate, although minor errors or omissions crop up. Thus, in the chapter on the parathyroids it is stated that the protein-bound blood calcium level is dependent on the total protein of the plasma rather than mainly on the albumin fraction. In the chapter on the thyroid gland, discussion is omitted of the physiology and pathologic physiology of exophthalmos and its possible relationship to the pituitary. In the chapter on the pituitary, emphasis is given to the work of Keller concerning the rôle of the different anatomical portions of the gland and the stalk, although this work has not been definitely confirmed. However, these criticisms are all minor and the book is highly recommended for the use of practitioner and student.

S. C. W.

Practical Physiological Chemistry. By Philip B. Hawk, PH.D., Bernard L. Oser, PH.D. and William H. Summerson, PH.D. 12th Edition. Pp. 1,323, with 329 illustrations and 5 color plates. Philadelphia, 1947. The Blakiston Company. *Price* $10.00.

The twelfth edition of this well known textbook and laboratory manual brings the subject matter up-to-date while preserving the time-tried plan of preceding editions. The text has been completely rewritten. New additions include sections on polarography, the theory and practice of photometric analysis, the Warburg tissue-slice technic, electrophoretic fractionation of plasma proteins, sulfonamides and antibiotics, composition of foods; and many new tests, experiments and quantitative procedures for blood and urine. Dr. Summerson, associate professor of biochemistry at Cornell University Medical College, appears as co-author for the first time in this edition and assumed a major rôle in the revision.

The text is divided into thirty-six chapters, the first seven introducing the physicochemical properties of solutions and the biochemical characteristics of carbohydrates, fats and proteins. Subsequent chapters deal with blood, urine and feces, the metabolic processes, and the various secretions and excretions of the body. Concise but sufficiently detailed laboratory experiments, tests and quantitative methods are given, each chapter concluding with a bibliography of selected references. An appendix furnishes details of preparation of reagents and solutions, together with tables listing the composition of foods and other useful data. Illustrations, graphs, tables and structural formulas are profusely scattered throughout the text. The paper is of good quality, the format is attractive, the typography is eminently readable, the volume is tastefully and sturdily bound and the index is adequate. Few typographical errors were noted.

The present edition assures the continued place of this book as a laboratory manual, teaching text and reference volume.

A. B. G.

Quantitative Clinical Chemistry. Interpretations. By John P. Peters, M.D. and Donald D. Van Slyke, PH.D., SC.D. Second edition, volume 1, pp. 1,041 with 62 figures, 40 tables. Baltimore, 1946. The Williams and Wilkins Company. *Price* $7.00.

This is the initial volume of the second edition, completely rewritten and reset, of a classic work which first appeared in 1931 and set a new standard of scholarship in the field. The second edition, like the first, will be divided into separate volumes dealing successively with "Interpretations" and "Methods"; but such has been the growth of the subject that, in order to treat the material in the desired detail, it has been found necessary to subdivide "Interpretations" into two volumes, of which this is the first.

Volume I begins with an introductory consideration of what is termed energy metabolism, the over-all energy changes of the body, and then proceeds with a detailed consideration of the chemistry and metabolism of carbohydrates, lipids and proteins. The discussion of carbohydrates is divided into extensive sections on chemistry, physiology and clinical aspects. The comprehensive chapter on lipids is supplemented with sections on steroid hormones and fat-soluble vitamins. Part IV, dealing with protein metabolism, is subdivided into sections dealing successively with the net metabolism of proteins, the amino acids, urea, ammonia, creatin and creatinine, purines and pyrimidines. Each section is followed by a large bibliography, most containing over 200 selected references and one exceeding 700. Scattered throughout the text are numerous tables and figures, many illustrating the results of key investigations, others graphically or in tabular form summarizing metabolic pathways and other complex material. The paper is of good quality considering the exigencies of the times, the format and typography are agreeable, and the volume is attractively and sturdily bound and adequately indexed.

While entitled a clinical chemistry, the exposition of this first volume is broader than is implied. The text properly deals at length with the biochemical and physiologic status of the normal subject, and this background is then integrated, so far as possible, with what is known of the changes observed in abnormal states. The treatment, moreover, gives sufficient historical perspective to indicate the chronologic development of ideas and thus attaches to the facts more meaning than would mere compilation. The whole makes a scholarly treatise, both in concept and accomplishment.

Dr. Peters indicates in his preface the difficulty in keeping the book abreast of expanding knowledge in so broad a field. Some of the chapters and bibliographies illustrate the difficulties involved.

A. B. G.

Penicillin: Its Practical Application. By various British authors under the editorship of Sir Alexander Fleming. Pp. 362 with 59 illustrations. Philadelphia, 1946. The Blakiston Company. *Price* $7.00.

"Penicillin: Its Practical Application," a symposium on penicillin by more than twenty British authors, is an excellent review of most aspects of the topic. Under the editorship of Sir Alexander Fleming, who has written the chapters on History and Bacteriological Control himself, various British authorities have contributed articles on Manufacture and Chemistry, Pharmacology, and Methods of Administration. There are, as well, twenty chapters on the use of penicillin in the specific clinical conditions in which it has been found to be of value, including such topics as Chest Infections, Wounds and Gas Gangrene, Hand Infections, Obstetrics and Gynecology, Venereal Diseases and so forth. The emphasis throughout is on practical considerations and for this reason it should be particularly valuable to the practitioner and medical student who will find the material in no textbook and who would be completely snowed under by the huge literature on the

subject. The general principles governing the use of penicillin are very well covered, but of necessity a book of this size can neither cover the field entirely nor provide an inclusive bibliography. Most references are naturally to the British literature.

The book suffers somewhat from repetition, but this is unavoidable when contributors independently submit articles on closely allied topics. Though one might differ with occasional statements made by some of the authors, there is no question but that on the whole the discussions are authoritative and fairly complete.

Practical Malariology. Prepared under the Auspices of the Division of Medical Science of the National Research Council, by Paul F. Russell, M.D., H.P.H., Luther S. West, PH.D. and Reginald D. Manwell, SC.D. Cloth, 684 pages with 238 illustrations, 8 in color. Philadelphia, 1946. W. B. Saunders. *Price* $8.00.

The practical aspects of malariology have been well presented by the authors, Russell, West and Manwell. The senior author, especially, is well versed in the subject, having devoted his still active career exclusively to malaria, chiefly in the field. From the standpoint of need during the war, it was too bad that this text was not available sooner, as there were many who could have used the information to great advantage. On the other hand, the delay has been compensated for by the inclusion of much material discovered during the war.

The material is well arranged under six sections which include the parasite, mosquito, man, community, prophylaxis and control, and therapeutic malaria. Particularly noticeable is the outstanding selection of excellent photographic illustrations. Although somewhat sketchy in a few parts, the contents as a whole form an important contribution to the library of anyone interested in malariology.

L. T. C.

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Volume III

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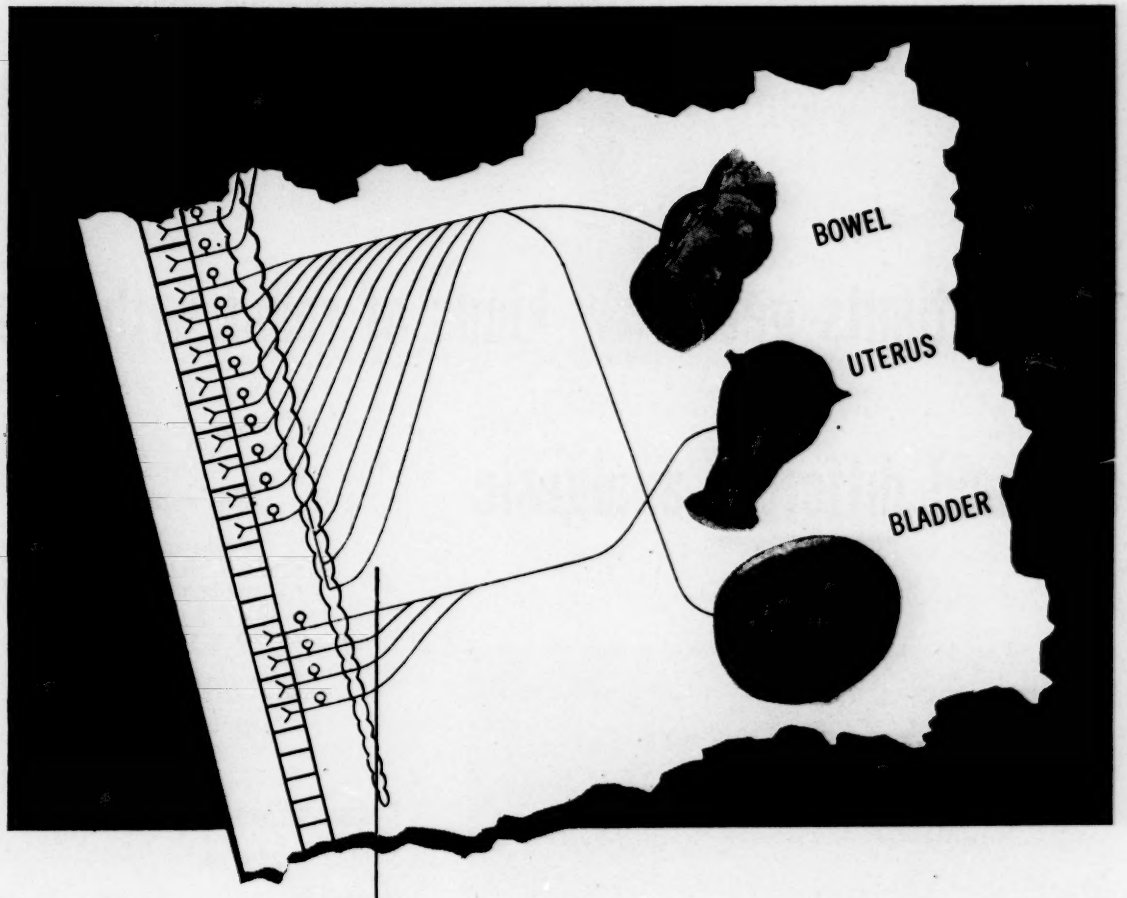

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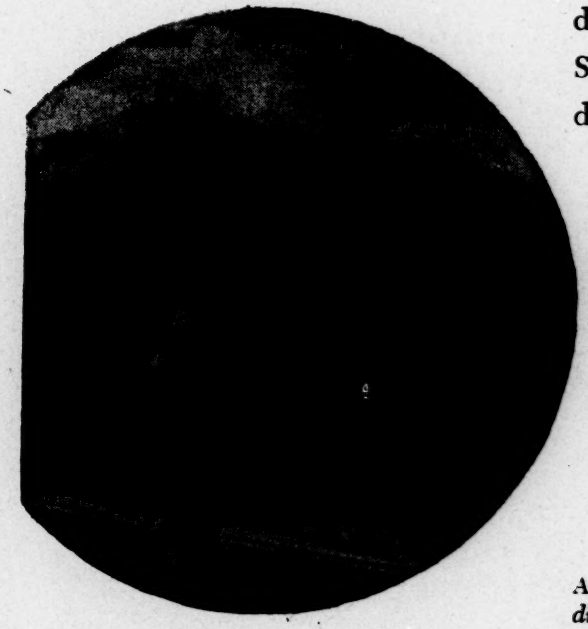

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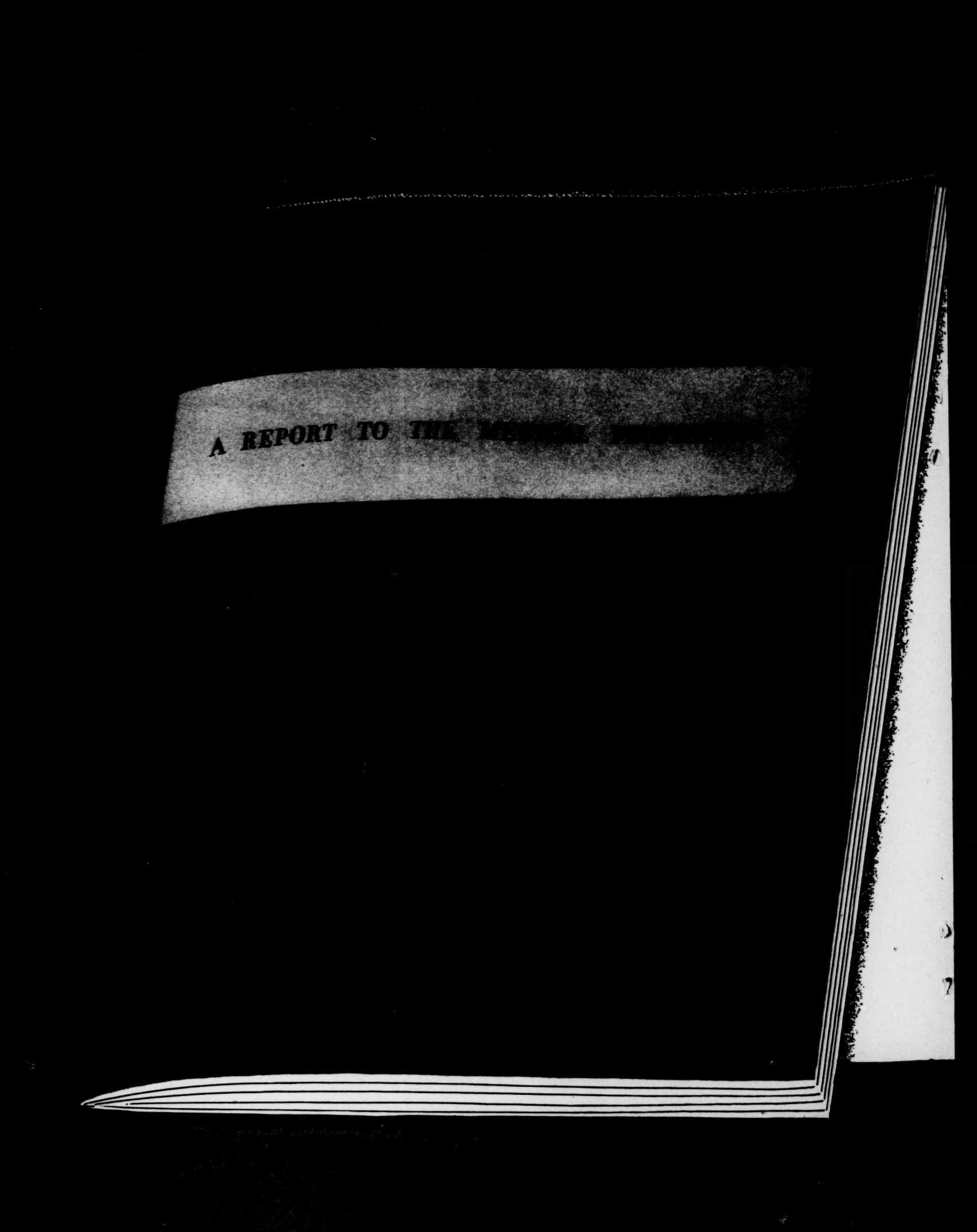
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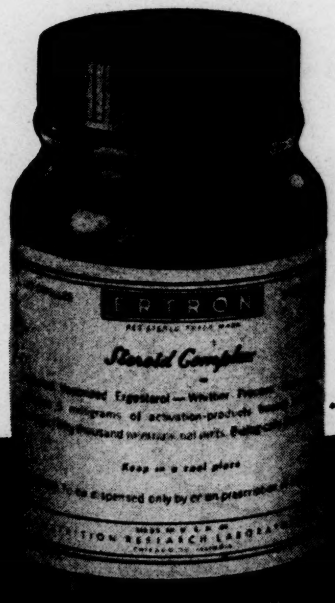

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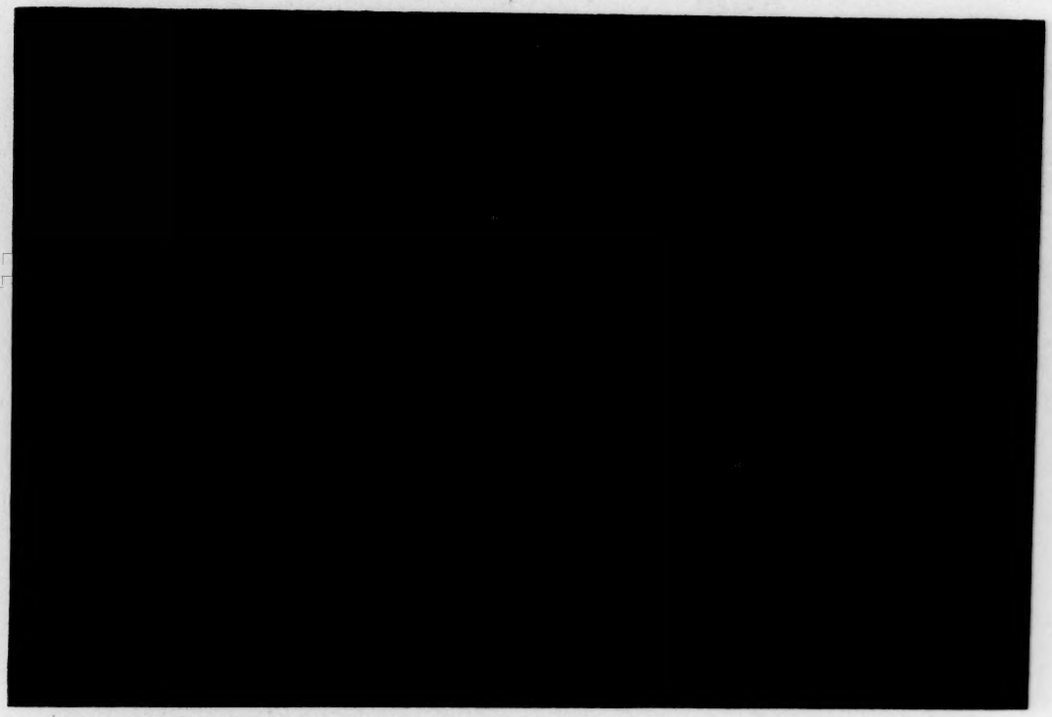

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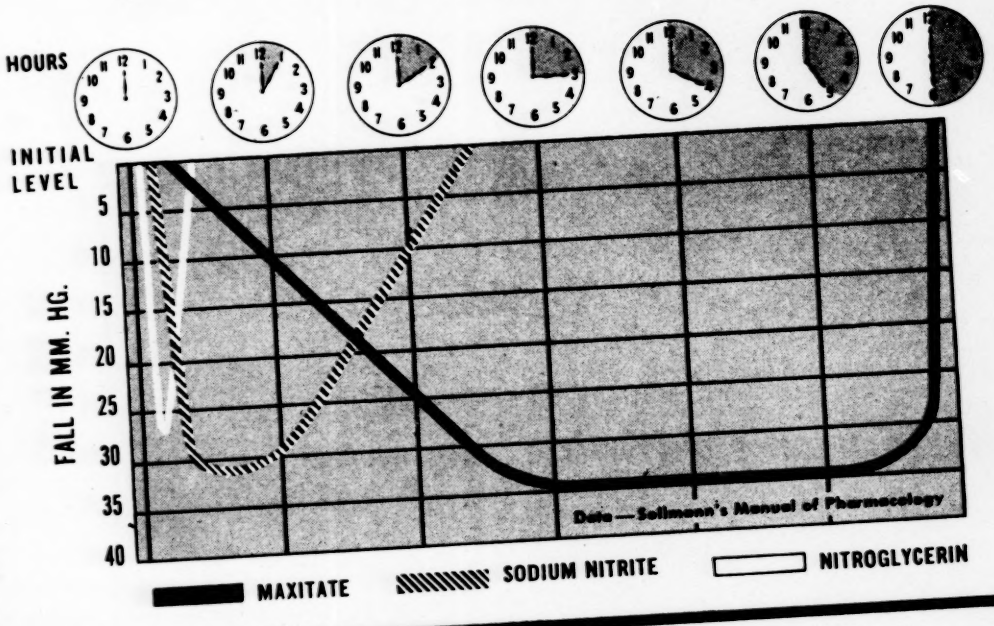

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Not only does Dexedrine produce striking improvement in mood and outlook—but, because of the unique "smoothness" of its action, it spares the patient the disturbing consciousness of "drug stimulation."
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Dexedrine*

Sulfate elixir tablets

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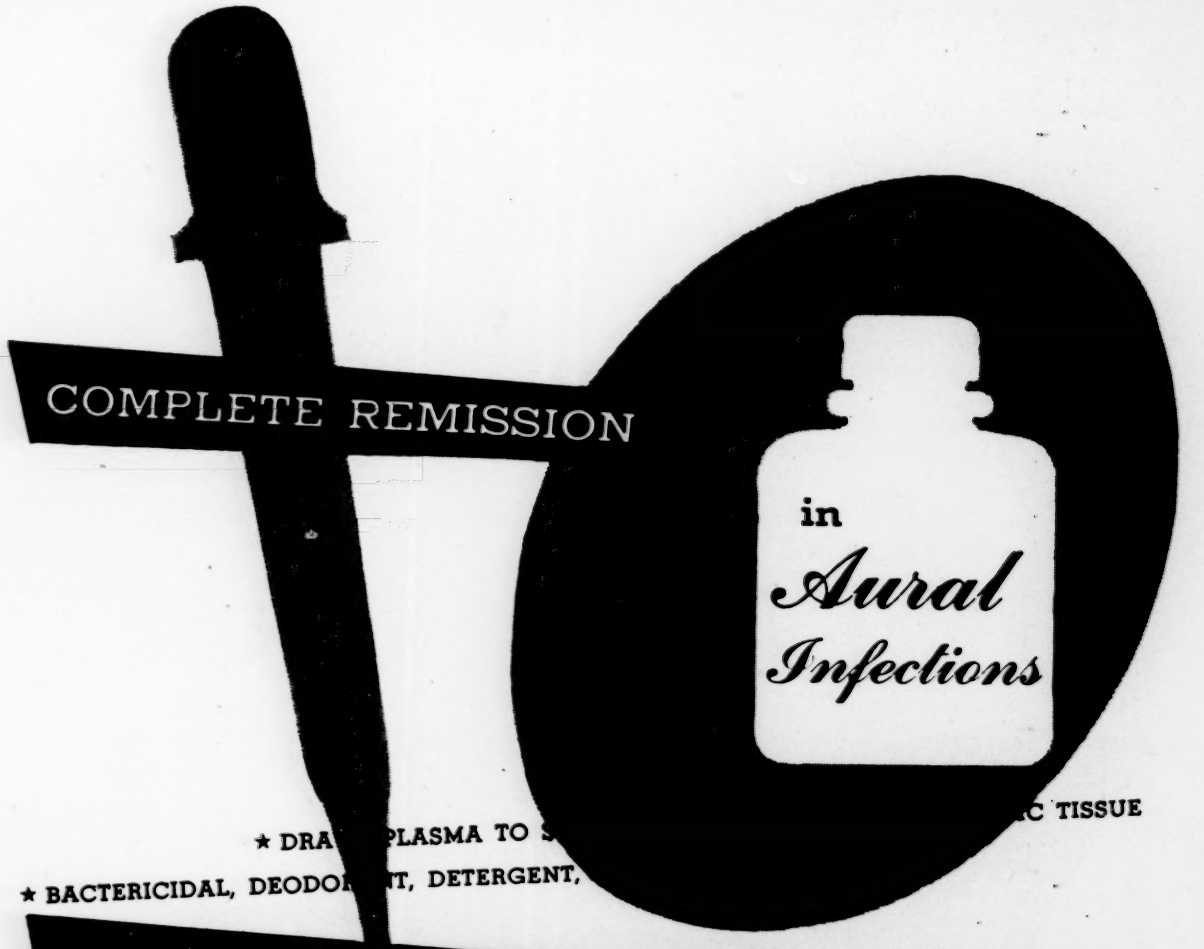
*T.M. REG. U.S. PAT. OFF.



Glycerite of Hydrogen Peroxide *the* With Carbamide

Clinical studies concerned with the use of Glycerite of Hydrogen Peroxide in the treatment of chronic purulent otitis media demonstrated seventeen of twenty-nine patients in complete remission in 14 days and the remainder by the 38th day. The patients studied presented conditions existent for periods of 2 weeks to over 40 years. Previous treatment by the usual therapeutic means, including tyrothricin or penicillin, was ineffective in all cases.

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Literature on request.

Constituents:

Hydrogen Peroxide 1.446%, Urea (Carbamide) 2.554%, 8-Hydroxyquinoline 0.1%. Dissolved and stabilized in substantially anhydrous glycerol . . . q.s. ad. 30cc.

Available on prescription in one-ounce bottle with dropper.
Administration: One-half dropperful two to four times daily.

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